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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Dec 17  The CA Lexicon available in the CAPLUS and CA files
 NEWS  3  Feb 06  Engineering Information Encompass files have new names
 NEWS  4  Feb 16  TOXLINE no longer being updated
 NEWS  5  Apr 23  Search Derwent WPINDEX by chemical structure
 NEWS  6  Apr 23  PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
 NEWS  7  May 07  DGENE Reload
 NEWS  8  Jun 20  Published patent applications (A1) are now in USPATFULL
 NEWS  9  JUL 13  New SDI alert frequency now available in Derwent's
                  DWPI and DPCI
 NEWS 10  Aug 23  In-process records and more frequent updates now in
                  MEDLINE
 NEWS 11  Aug 23  PAGE IMAGES FOR 1947-1966 RECORDS IN CAPLUS AND CA
 NEWS 12  Aug 23  Adis Newsletters (ADISNEWS) now available on STN
 NEWS 13  Sep 17  IMSworld Pharmaceutical Company Directory name change
                  to PHARMASEARCH

 NEWS EXPRESS  August 15 CURRENT WINDOWS VERSION IS V6.0c,
               CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP),
               AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001
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                                                       ENTRY    SESSION
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=> s haparanase (5N) antibod?
L1            0 HAPARANASE (5N) ANTIBOD?

=> s heparanase (5N) antibod?
L2           53 HEPARANASE (5N) ANTIBOD?

=> s l2 (10N) (endogenous or natural)
L3            0 L2 (10N) (ENDOGENOUS OR NATURAL)

=> dup rem l2
PROCESSING COMPLETED FOR L2
L4           23 DUP REM L2 (30 DUPLICATES REMOVED)

=> dis l4 1-23 ibib abs kwic

L4   ANSWER 1 OF 23  CAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         2001:229058  CAPLUS
DOCUMENT NUMBER:          134:262849
TITLE:                    Human heparanase-2, its sequence, recombinant
                          production, and use in identifying potential
                          antagonists and/or agonists
INVENTOR(S):              Duecker, Klaus; Sirrenberg, Christian
PATENT ASSIGNEE(S):       Merck Patent G.m.b.H., Germany
SOURCE:                   PCT Int. Appl., 46 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ----------------  ----  --------      ---------------  --------
     WO 2001021814      A1   20010329      WO 2000-EP8837   20000911
         W:  CA, JP, US
         RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE
PRIORITY APPLN. INFO.:                    EP 1999-118805   A  19990923
                                          EP 2000-114649   A  20000707
AB   The invention provides a cDNA mol. encoding a human protein believed to be
     heparanase-2, based on sequence homol. to known heparanases.  The
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invention also provides polynucleotides that contain fragments of said cDNA mols. that can be used as hybridization probes or as primers for nucleic acid amplification. The invention further provides expression vectors comprising said cDNA mols., host cells transformed with said vectors for the recombinant prodn. of human heparanase-2. Still further, the invention provides for the use of said human heparanase-2 polypeptides in identifying compds. that may be antagonists and/or agonists, which may be potentially useful in therapy. Finally, the invention provides a fusion protein consisting of said heparanase-2 fused to a Ig Fc region, and **antibodies** specific for **heparanase**-2. The cDNA sequence, as well as the corresponding amino acid sequence of human heparanase-2 are claimed. The invention used reverse transcription-polymerase chain reaction (RT-PCR) to show the expression of heparanase-2 gene in various tissues and tumors, and showed the expression of heparanase-2 in transformed 293 human kidney fibroblasts.

REFERENCE COUNT: 6

REFERENCE(S):
(1) Fairbanks, M; WO 9943830 A 1999 CAPLUS
(2) Hadasit Med Res Service; WO 9911798 A 1999 CAPLUS
(3) Hamdorf, B; WO 9921975 A 1999 CAPLUS
(4) Kosir, M; JOURNAL OF SURGICAL RESEARCH 1997, V67(1), P98 CAPLUS
(5) Kosir, M; JOURNAL OF SURGICAL RESEARCH 1999, V81(1), P42 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The invention provides a cDNA mol. encoding a human protein believed to be heparanase-2, based on sequence homol. to known heparanases. The invention also provides polynucleotides that contain fragments of said cDNA mols. that can be used as hybridization probes or as primers for nucleic acid amplification. The invention further provides expression vectors comprising said cDNA mols., host cells transformed with said vectors for the recombinant prodn. of human heparanase-2. Still further, the invention provides for the use of said human heparanase-2 polypeptides in identifying compds. that may be antagonists and/or agonists, which may be potentially useful in therapy. Finally, the invention provides a fusion protein consisting of said heparanase-2 fused to a Ig Fc region, and **antibodies** specific for **heparanase**-2. The cDNA sequence, as well as the corresponding amino acid sequence of human heparanase-2 are claimed. The invention used reverse transcription-polymerase chain reaction (RT-PCR) to show the expression of heparanase-2 gene in various tissues and tumors, and showed the expression of heparanase-2 in transformed 293 human kidney fibroblasts.

IT **Antibodies**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(anti-human **heparanase** 2 specific **antibodies**)

L4 ANSWER 2 OF 23 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:12473 CAPLUS
DOCUMENT NUMBER: 134:96257
TITLE: Protein and cDNA sequences of a novel human heparanase gene hnhpl and its splicing variants
INVENTOR(S): Pecker, Iris; Michal, Israel; Itzhaki, Hanan
PATENT ASSIGNEE(S): Insight Strategy & Marketing Ltd., Israel
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000643	A2	20010104	WO 2000-IL358	20000619

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-140801 P 19990625

AB The invention provides protein and cDNA sequences of a novel human heparanase gene hnhpl and two variants resulted from alternative splicing. The longest clone is 2060 nucleotide long and it contains an open reading frame of 1776 nucleotides, which encodes a polypeptide of 592 amino acids, with a calcd. mol. wt. of 66.5 kDa. The two shorter forms contain an in frame deletion as a result of alternative splicing, one is 162 nucleotides (nt473~634) corresponding to amino acids 150-203, and one is 336 nucleotides (nt473-808) corresponding to amino acids 150-261. The hnhpl gene is mapped to chromosome 10, next to the marker SHGC-57721. The tissue distribution of hnhpl transcripts is detd. The invention also relates to constructing hnhpl gene expression vector to produce recombinant proteins in mammalian cells, which may have heparanase or other glycosyl hydrolase activity, its antibodies, and antisense oligonucleotide and ribozymes for gene modulation and therapeutic use.

REFERENCE COUNT: 52

REFERENCE(S):
(2) Bashkin, P; Biochemistry 1989, V28, P1737 CAPLUS
(3) Burgess, W; Annu Rev Biochem 1989, V58, P575 CAPLUS
(5) Chen, Y; Nature Medicine 1997, V3, P866 CAPLUS
(7) Durand, P; Glycobiology 1997, V7(2), P277 CAPLUS
(8) Eisenberg, S; J Clin Invest 1992, V90, P2013 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT **Antibodies**
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(to **heparanase** encoded by gene hnhpl; protein and cDNA sequences of a novel human heparanase gene hnhpl and splicing variants)

L4 ANSWER 3 OF 23 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:57239 CAPLUS
DOCUMENT NUMBER: 134:128217
TITLE: Heparanase specific molecular probes and their use in research and medical applications
INVENTOR(S): Pecker, Iris; Vlodavsky, Israel; Friedman, Yael; Perets, Tuvia
PATENT ASSIGNEE(S): Insight Strategy & Marketing Ltd., Israel
SOURCE: U.S., 41 pp., Cont.-in-part of U.S. 5,968,822.
CODEN: USXXAM
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6177545	B1	20010123	US 1998-71739	19980501
US 5968822	A	19991019	US 1997-922170	19970902
WO 9957153	A1	19991111	WO 1999-US9255	19990429

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9938706.	A1	19991123	AU 1999-38706	19990429
EP 1073682	A1	20010207	EP 1999-921513	19990429

R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE, IE, FI

NO 9906229	A	20000224	NO 1999-6229	19991215

PRIORITY APPLN. INFO.:
US 1997-922170 A2 19970902
US 1998-71739 A 19980501
WO 1999-US9255 W 19990429

AB A variety of heparanase specific mol. probes which can be used for research and medical applications including diagnosis and therapy. Specific applications include the use of a heparanase specific mol. probe for detection of the presence, absence or level of heparanase expression; the use of a heparanase specific mol. probe for therapy of a condition assocd. with expression of heparanase; the use of a heparanase specific mol. probe for quantification of heparanase in a body fluid; the use of a heparanase specific mol. probe for targeted drug delivery; and the use of a heparanase specific mol. probe as a therapeutic agent.

REFERENCE COUNT: 23
REFERENCE(S):
(1) Burgess; Annu Rev Biochem 1989, V58, P575 CAPLUS
(4) Folkman; Science 1987, V235, P442 CAPLUS
(6) Fuks; US 5362641 1994 CAPLUS
(9) Jackson; Physiological Reviews 1991, V71(2), P481 CAPLUS
(10) Kjellen; Annu Rev Biochem 1991, V60, P443 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

ST **heparanase** probe **antibody**; sequence gene human heparanase

IT **Antibodies**
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(**heparanase**-specific mol. probes and their use in research and medical applications)

IT **Antibodies**
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(monoclonal; **heparanase**-specific mol. probes and their use in research and medical applications)

L4 ANSWER 4 OF 23 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001252356 MEDLINE
DOCUMENT NUMBER: 21248515 PubMed ID: 11350898
TITLE: The clinicopathological significance of heparanase and basic fibroblast growth factor expressions in hepatocellular carcinoma.
AUTHOR: El-Assal O N; Yamanoi A; Ono T; Kohno H; Nagasue N
CORPORATE SOURCE: The Second Department of Surgery, Shimane Medical University, Izumo 693-8501, Japan.
SOURCE: CLINICAL CANCER RESEARCH, (2001 May) 7 (5) 1299-305.
Journal code: C2H; 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

AB Heparan sulfate plays an essential role for insolubility of the components of extracellular matrix and represents a storage depot for various growth factors. Therefore, heparanase produced by a given tumor may facilitate tumor invasiveness and angiogenesis through the release of heparan sulfate-bound growth factors. Although the growth factors responsible for angiogenesis in hepatocellular carcinoma (HCC) have recently been investigated, the clinicopathological significance of heparanase in connection with basic fibroblast growth factor (bFGF) expression in HCC has not been evaluated so far. Fifty-five patients who had undergone hepatic resection for HCC without preoperative treatment were included in the present study. Expression of heparanase mRNA was evaluated by reverse transcription-PCR, and bFGF was examined by Western blotting using a monoclonal antibody. Tumor angiogenesis was evaluated by immunostaining with a factor VIII-related monoclonal **antibody**. Expression of **heparanase** mRNA was detected in 47% of HCCs and was significantly correlated with larger tumor size (P = 0.01), presence of portal vein invasion (P = 0.01), and higher overall tumor invasiveness (P = 0.02). Moreover, its expression was correlated with tumor microvessel density (MVD; P = 0.02). There was a direct correlation between the levels of bFGF proteins and MVD in HCCs (P = 0.0001), and, furthermore, concomitant expression of bFGF and heparanase was associated with higher tumor MVD as compared with expression of either factor alone (P = 0.01). In conclusion, the expression of heparanase in HCC enhances growth, invasion, and angiogenesis of the tumor, and bFGF seems to be a potent angiogenic factor for HCC.

AB . . . was examined by Western blotting using a monoclonal antibody. Tumor angiogenesis was evaluated by immunostaining with a factor VIII-related monoclonal **antibody**. Expression of **heparanase** mRNA was detected in 47% of HCCs and was significantly correlated with larger tumor size (P = 0.01), presence of. . .

L4 ANSWER 5 OF 23 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001252533 MEDLINE
DOCUMENT NUMBER: 21248752 PubMed ID: 11351242
TITLE: Expression of heparanase, Mdm2, and erbB2 in ovarian cancer.
AUTHOR: Ginath S; Menczer J; Friedmann Y; Aingorn H; Aviv A; Tajima K; Dantes A; Glezerman M; Vlodavsky I; Amsterdam A
CORPORATE SOURCE: Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel.
SOURCE: INTERNATIONAL JOURNAL OF ONCOLOGY, (2001 Jun) 18 (6)

1133-44.
Journal code: CX5; 9306042. ISSN: 1019-6439.
PUB. COUNTRY: Greece
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010730
Last Updated on STN: 20010730
Entered Medline: 20010726

AB Ovarian cancer is the most lethal of gynecological malignancies. Yet early diagnosis and prognosis are far from being satisfactory. Degradation of heparan sulfate proteoglycans by heparanase appears to play an important role in the invasiveness of tumor cells through the basement membrane and into the extracellular matrix. Recent cloning of the **heparanase** gene and generation of monoclonal **antibodies** against the enzyme permit to examine tumor cell expression of the enzyme. The aim of the present study was to assess heparanase activity and localization in various subtypes of epithelial ovarian cancer in correlation with oncogene expression. Histologically confirmed malignant ovarian tissue from ten women and tissue from 2 benign ovarian tumors and 4 normal ovaries were assessed for heparanase presence, activity and localization, incidence of apoptosis and expression of the oncogenes erbB2 and Mdm2. Heparanase immunohistostaining and activity were present in mucinous carcinomas and were more intense than in endometrioid and in serous carcinomas. The lowest activity was observed in benign ovarian tumors and normal ovaries. In ovarian carcinomas the enzyme was intensely concentrated in the cytoplasm of the cancerous cells. In contrast, in normal ovaries and benign tumors the enzyme was predominantly localized in endothelial cells lining blood capillaries. The rate of apoptosis was considerably higher in mucinous and endometrioid carcinomas, and was lower in serous and primary peritoneal carcinomas. Extremely high concentration of heparanase was often demonstrated in apoptotic cells. Endometrioid and serous carcinomas showed high expression of Mdm2 and erbB2 while mucinous carcinomas showed low expression. In benign ovarian tumors and normal ovaries the expression of both oncoproteins was extremely low. In conclusion ovarian carcinomas demonstrate higher levels of heparanase than benign tumors and normal ovaries suggesting that the enzyme may play an important role in metastatic spread of the cancerous cells. Apoptosis may be a significant part of the mechanism of the enzyme release into the extracellular space. Although heparanase activity seems to play an essential role in tumor progression, expression of oncogenes, such as erbB2 and Mdm2 seems to play the dominant role in the development of ovarian cancer.

AB . . . role in the invasiveness of tumor cells through the basement membrane and into the extracellular matrix. Recent cloning of the **heparanase** gene and generation of monoclonal **antibodies** against the enzyme permit to examine tumor cell expression of the enzyme. The aim of the present study was to. . .

L4 ANSWER 6 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:900837 CAPLUS
DOCUMENT NUMBER: 134:38857
TITLE: Heparanase assay using an immobilized heparan sulfate glycosaminoglycan and a paracrine cell regulator
INVENTOR(S): Brenchley, Paul Ernest Charles
PATENT ASSIGNEE(S): Central Manchester Healthcare NHS Trust, UK
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000077241	A2	20001221	WO 2000-GB2117	20000612
WO 2000077241	A3	20010322		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 1999-13415 A 19990610
AB A method of assaying a sample to det. heparanase activity thereof comprises the steps of (i) incubating the sample in the presence of a first solid phase support having immobilized thereon an heparan sulfate glycosaminoglycan (HSGAG) polymer substrate for the heparanase, the said substrate being insensitive to the action of proteases and the said substrate having bonded thereto a first binding moiety and having further bonded thereto a paracrine cell regulator (such as cytokine, chemokine or growth factor) capable of binding to HSGAG, (ii) treating the incubated sample with a second solid phase support having a second moiety provided thereon capable of immobilizing HSGAG polymer substrate cleaved from the first solid phase support on said second solid phase support by binding of said second moiety either with the paracrine cell regulator or with the first binding moiety, (iii) generating a measurable signal the other of the first or second moiety of the cleaved substrate immobilized in the second support solid phase, and (iv) measuring the signal on the second solid phase support sepd. from the first solid phase support.
IT 9003-99-0, Peroxidase
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(**antibody** coupled with; **heparanase** detn. using immobilized heparan sulfate glycosaminoglycan and paracrine cell regulator)

L4 ANSWER 7 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:314574 CAPLUS
DOCUMENT NUMBER: 132:333392
TITLE: **Heparanase** activity neutralizing anti-**heparanase** monoclonal **antibody**
INVENTOR(S): Peretz, Tuvia; Miron, Daphna; Shlomi, Yinon; Pecker, Iris; Ayal-Hershkovitz, Maty; Friedman, Yael; Vlodavsky, Israel
PATENT ASSIGNEE(S): Insight Strategy & Marketing Ltd., Israel; Hadasit Medical Research Services & Development Ltd.; Friedman, Mark M.
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000025817	A1	20000511	WO 1999-US25451	19991028
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1126878	A1	20010829	EP 1999-956781	19991028
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 2001002190	A	20010612	NO 2001-2190	20010503

PRIORITY APPLN. INFO.: US 1998-186200 A 19981104
WO 1999-US25451 W 19991028

AB A monoclonal **antibody** elicited by a **heparanase** protein or an immunogenic portion thereof, the monoclonal **antibody** specifically inhibits **heparanase** activity. The **heparanase**-specific monoclonal **antibody** may be human or humanized antibody and is useful for treating conditions assocd. with altered function of a heparan sulfate proteoglycan-assocd. biol. effector mol. such as growth factor, chemokine, cytokine and degradative enzyme. The condition is selected from the group consisting of angiogenesis, cell proliferation, tumor, metastasis, inflammatory disorders and autoimmune conditions.

REFERENCE COUNT: 6
REFERENCE(S):
(1) Anon; WO 9201003 A1 1992 CAPLUS
(2) Fuks; US 5362641 A 1994 CAPLUS
(3) Jin, L; Internat J Cancer 1990, V45, P1088 CAPLUS
(4) Lider, O; Eur J Immunol 1990, V20, P493 CAPLUS
(5) Parish, C; Immunol Cell Biol 1998, V76, P104 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Heparanase** activity neutralizing anti-**heparanase** monoclonal **antibody**

AB A monoclonal **antibody** elicited by a **heparanase** protein or an immunogenic portion thereof, the monoclonal **antibody** specifically inhibits **heparanase** activity. The **heparanase**-specific monoclonal **antibody** may be human or humanized antibody and is useful for treating conditions assocd. with altered function of a heparan sulfate proteoglycan-assocd. biol. effector mol. such as growth factor, chemokine, cytokine and degradative enzyme. The condition is selected from the group consisting of angiogenesis, cell proliferation, tumor, metastasis, inflammatory disorders and autoimmune conditions.

ST **heparanase** neutralizing monoclonal **antibody** tumor inflammation; autoimmune disease angiogenesis **heparanase** monoclonal **antibody**

IT Chemokines
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(IP-10; anti-**heparanase** monoclonal **antibody** for treating angiogenic conditions, tumors, inflammations, metastasis and autoimmune diseases)

IT Chemokines
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(MGSA; anti-**heparanase** monoclonal **antibody** for treating angiogenic conditions, tumors, inflammations, metastasis and autoimmune diseases)

IT Chemokines
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(PF-4; anti-**heparanase** monoclonal **antibody** for treating angiogenic conditions, tumors, inflammations, metastasis and autoimmune diseases)

IT Autoimmune disease
Drugs
Hybridoma
Inflammation
Neoplasm
(anti-**heparanase** monoclonal **antibody** for treating angiogenic conditions, tumors, inflammations, metastasis and autoimmune diseases)

IT Chemokines
Cytokines
Growth factors, animal
Interleukin 3
Interleukin 8
Lymphotoxin
Macrophage inflammatory protein 1.alpha.
Macrophage inflammatory protein 1.beta.
Monocyte chemoattractant protein-1
Neutrophil-activating peptide-2
RANTES (chemokine)
Tumor necrosis factors
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(anti-**heparanase** monoclonal **antibody** for treating angiogenic conditions, tumors, inflammations, metastasis and autoimmune diseases)

IT Enzymes, biological studies
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(degradative; anti-**heparanase** monoclonal **antibody** for treating angiogenic conditions, tumors, inflammations, metastasis and autoimmune diseases)

IT Angiogenesis
(disease; anti-**heparanase** monoclonal **antibody** for treating angiogenic conditions, tumors, inflammations, metastasis and autoimmune diseases)

IT Proteoglycans, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(heparitin sulfate-contg.; anti-**heparanase** monoclonal **antibody** for treating angiogenic conditions, tumors,

inflammations, metastasis and autoimmune diseases)

IT Epitopes
(mapping; anti-**heparanase** monoclonal **antibody** for treating angiogenic conditions, tumors, inflammations, metastasis and autoimmune diseases)

IT Neoplasm
(metastasis; anti-**heparanase** monoclonal **antibody** for treating angiogenic conditions, tumors, inflammations, metastasis and autoimmune diseases)

IT **Antibodies**
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(monoclonal, human or humanized; anti-**heparanase** monoclonal **antibody** for treating angiogenic conditions, tumors, inflammations, metastasis and autoimmune diseases)

IT **Antibodies**
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(monoclonal, neutralizing; anti-**heparanase** monoclonal **antibody** for treating angiogenic conditions, tumors, inflammations, metastasis and autoimmune diseases)

IT Disease, animal
(proliferative; anti-**heparanase** monoclonal **antibody** for treating angiogenic conditions, tumors, inflammations, metastasis and autoimmune diseases)

IT Interferons
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(.gamma.; anti-**heparanase** monoclonal **antibody** for treating angiogenic conditions, tumors, inflammations, metastasis and autoimmune diseases)

IT 89800-66-8, **Heparanase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(anti-**heparanase** monoclonal **antibody** for treating angiogenic conditions, tumors, inflammations, metastasis and autoimmune diseases)

IT 9004-02-8, Lipoprotein lipase 9004-06-2, Elastase 12629-01-5, Human growth hormone 56645-49-9, Cathepsin G 62031-54-3, FGF 83869-56-1, GM-CSF 127464-60-2, Vascular endothelial growth factor
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-**heparanase** monoclonal **antibody** for treating angiogenic conditions, tumors, inflammations, metastasis and autoimmune diseases)

L4 ANSWER 8 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:53938 CAPLUS
DOCUMENT NUMBER: 132:102821
TITLE: Method of screening for potential anti-metastatic and anti-inflammatory agents using mammalian heparanase as a probe
INVENTOR(S): Ben-Artzi, Hanna; Ayal-Hershkovitz, Maty; Vlodavsky, Israel; Pecker, Iris; Peleg, Yoav; Miron, Daphna
PATENT ASSIGNEE(S): Insight Strategy & Marketing Ltd., Israel; Hadasit Medical Research Services & Development Ltd.; Friedman, Mark M.
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000003036	A1	20000120	WO 1999-US15643	19990712
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6190875	B1	20010220	US 1998-113168	19980710
AU 9948697	A1	20000201	AU 1999-48697	19990712
EP 1097241	A1	20010509	EP 1999-932382	19990712
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 2001000136	A	20010309	NO 2001-136	20010109

PRIORITY APPLN. INFO.: US 1998-113168 A 19980710
US 1997-922170 A2 19970902
US 1998-109386 B2 19980702
WO 1999-US15643 W 19990712

AB Qual. and quant. methods are provided for testing an agent for its potential at inhibiting glycosidase catalytic activity, the methods including interacting a glycosidase enzyme with a glycosidase substrate in a presence of the agent and qual. or quant. evaluating an effect of the agent on the catalytic activity of the glycosidase enzyme toward the glycosidase substrate. Preferably the glycosidase enzyme is a heparanase enzyme and the glycosidase substrate is, resp., a heparanase substrate.

REFERENCE COUNT: 7
REFERENCE(S): (2) Fuks; US 5362641 A 1994 CAPLUS
(3) Gallo; US 5129877 A 1992 CAPLUS
(4) Leshchiner; US 5399351 A 1995 CAPLUS
(5) Lormeau; US 5550116 A 1996 CAPLUS
(6) Nicholson; US 4859581 A 1989 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT **Antibodies**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-**heparanase**; antimetastatic and antiinflammatory agent screening with heparanase probe)

L4 ANSWER 9 OF 23 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001009022 MEDLINE
DOCUMENT NUMBER: 20476203 PubMed ID: 11021821
TITLE: Expression of heparanase in normal, dysplastic, and neoplastic human colonic mucosa and stroma. Evidence for its role in colonic tumorigenesis.
AUTHOR: Friedmann Y; Vlodavsky I; Aingorn H; Aviv A; Peretz T; Pecker I; Pappo O
CORPORATE SOURCE: Departments of Oncology and Pathology, Hadassah-Hebrew

University Hospital, Jerusal nd InSight Ltd., Rabin Science Park, Rehovot, Israel.
SOURCE: AMERICAN JOURNAL OF PATHOLOGY, (2000 Oct) 157 (4) 1167-75. Journal code: 3RS. ISSN: 0002-9440.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001025

AB The human heparanase gene, an endo-beta-glucuronidase that cleaves heparan sulfate at specific intrachain sites, has recently been cloned and shown to function in tumor progression and metastatic spread. Antisense digoxigenin-labeled heparanase RNA probe and monoclonal anti-human **heparanase antibodies** were used to examine the expression of the heparanase gene and protein in normal, dysplastic, and neoplastic human colonic mucosa. To our knowledge, this is the first systematic study of heparanase expression in human colon cancer. Both the heparanase gene and protein were expressed at early stages of neoplasia, already at the stage of adenoma, but were practically not detected in the adjacent normal-looking colon epithelium. Gradually increasing expression of heparanase was evident as the cells progressed from severe dysplasia through well-differentiated to poorly differentiated colon carcinoma. Deeply invading colon carcinoma cells showed the highest levels of the heparanase mRNA and protein associated with expression of both the gene and enzyme by adjacent desmoplastic stromal fibroblasts. A high expression was also found in colon carcinoma metastases to lung, liver, and lymph nodes, as well as in the accompanying stromal fibroblasts. Moreover, extracts derived from tumor tissue expressed much higher levels of the heparanase protein and activity as compared to the normal colon tissue. In all specimens, the heparanase gene and protein exhibited the same pattern of expression. These results suggest a role of heparanase in colon cancer progression and may have both prognostic and therapeutic applications.

AB . . . been cloned and shown to function in tumor progression and metastatic spread. Antisense digoxigenin-labeled heparanase RNA probe and monoclonal anti-human **heparanase antibodies** were used to examine the expression of the heparanase gene and protein in normal, dysplastic, and neoplastic human colonic mucosa.. . .

L4 ANSWER 10 OF 23 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000229546 MEDLINE
DOCUMENT NUMBER: 20229546 PubMed ID: 10764835
TITLE: Heparanase expression in invasive trophoblasts and acute vascular damage.
AUTHOR: Dempsey L A; Plummer T B; Coombes S L; Platt J L
CORPORATE SOURCE: Department of Surgery, Mayo Clinic, Rochester, MN 55905, USA.
SOURCE: GLYCOBIOLOGY, (2000 May) 10 (5) 467-75. Journal code: BEL; 9104124. ISSN: 0959-6658.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF084467
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000518
Last Updated on STN: 20000518
Entered Medline: 20000505

AB Heparan sulfate proteoglycans play a pivotal role in tissue function, development, inflammation, and immunity. We have identified a novel cDNA encoding human heparanase, an enzyme thought to cleave heparan sulfate in physiology and disease, and have located the HEP gene on human chromosome 4q21. Monoclonal **antibodies** against human **heparanase** located the enzyme along invasive extravillous trophoblasts of human placenta and along endothelial cells in organ xenografts targeted by hyperacute rejection, both sites of heparan sulfate digestion. Heparanase deposition was evident in arterial walls in normal tissues; however, vascular heparan sulfate cleavage was coincident with heparanase enzyme during inflammatory episodes. These findings suggest that heparanase elaboration and control of catalytic activity may contribute to the development and pathogenesis of vascular disease and suggest that heparanase intervention might be a useful therapeutic target.

AB . . . thought to cleave heparan sulfate in physiology and disease, and have located the HEP gene on human chromosome 4q21. Monoclonal **antibodies** against human **heparanase** located the enzyme along invasive extravillous trophoblasts of human placenta and along endothelial cells in organ xenografts targeted by hyperacute. . .

L4 ANSWER 11 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:723147 CAPLUS
DOCUMENT NUMBER: 131:332967
TITLE: Genetically modified cells and methods for expressing recombinant heparanase and methods of purifying same
INVENTOR(S): Ben-Artzi, Hanna; Ayal-Hershkovitz, Maty; Yacoby-Zeevi, Oron; Pecker, Iris; Peleg, Yoav; Shlomi, Yinon
PATENT ASSIGNEE(S): Insight Strategy & Marketing Ltd., Israel; Friedman, Mark, M.
SOURCE: PCT Int. Appl., 118 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9957244	A1	19991111	WO 1999-US9256	19990429
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9937705	A1	19991123	AU 1999-37705	19990429
EP 1076689	A1	20010221	EP 1999-920135	19990429
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

NO 2000005100 A 20001228 NO [redacted]-5100 20001010
PRIORITY APPLN. INFO.: US 1998-71618 A 19980501
US 1999-260038 A 19990302
WO 1999-US9256 W 19990429

AB Bacterial, yeast and animal cells and methods for overexpressing recombinant heparanase in cellular systems, methods of purifying recombinant heparanase therefrom and modified heparanase species which serve as precursors for generating highly active heparanase by proteolysis. Heparanase is a glycosylated enzyme involved in catabolism of certain glycosaminoglycans, in tumor cell invasion and metastasis, and possibly in angiogenesis. It has potential therapeutic applications for viral infection, neurodegenerative diseases, restenosis, and atherosclerosis. A signal peptide was incorporated for effective protein secretion in yeast and bacteria and insect and mammalian cells. Protein secretion is achieved by induction by thrombin and calcium ionophores and immune complexes and antigens and mitogens. This work describes prodn. of heparanase on a biotechnol. scale of at least half a liter growth medium by affinity purifn. This large scale propagation of animal cells is described in a Spinner-basket bioreactor. The heparanase enzyme is activated by digestion with a protease such as cathepsin L or trypsin at appropriate pH. A correctly folded catalytically active heparanase is generated.

REFERENCE COUNT: 2
REFERENCE(S): (1) Insight Strategy & Marketing Ltd; WO 9911798 A1 1999 CAPLUS
(2) The Upjohn Co; WO 9504158 A1 1995 CAPLUS

IT **Antibodies**
RL: ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**heparanase**-specific; genetically modified cells and methods for expressing recombinant heparanase and methods of purifying same)

L4 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:723067 CAPLUS
DOCUMENT NUMBER: 131:350261
TITLE: Heparanase specific molecular probes and their use in research and medical applications
INVENTOR(S): Pecker, Iris; Vlodavsky, Israel; Friedman, Yael; Perets, Tuvia
PATENT ASSIGNEE(S): Insight Strategy & Marketing Ltd., Israel; Hadasit Medical Research Services & Development Ltd.; Friedman, Mark, M.
SOURCE: PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9957153	A1	19991111	WO 1999-US9255	19990429
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6177545	B1	20010123	US 1998-71739	19980501
AU 9938706	A1	19991123	AU 1999-38706	19990429
EP 1073682	A1	20010207	EP 1999-921513	19990429
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE, IE, FI				
NO 9906229	A	20000224	NO 1999-6229	19991215

PRIORITY APPLN. INFO.: US 1998-71739 A 19980501
US 1997-922170 A2 19970902
WO 1999-US9255 W 19990429

AB A variety of heparanase specific mol. probes which can be used for research and medical applications including diagnosis and therapy. Specific applications include the use of a heparanase specific mol. probe for detection of the presence, absence or level of heparanase expression; the use of a heparanase specific mol. probe for therapy of a condition assocd. with expression of heparanase; the use of a heparanase specific mol. probe for quantification of heparanase in a body fluid; the use of a heparanase specific mol. probe for targeted drug delivery; and the use of a heparanase specific mol. probe as a therapeutic agent.

REFERENCE COUNT: 14
REFERENCE(S): (2) Board Of Regents The University Of Texas System; WO 8801280 A1 1988 CAPLUS
(3) Fuks; US 5362641 A 1994 CAPLUS
(4) Gewirtz; US 5618709 A 1997 CAPLUS
(6) Jin; Int J Cancer 1990, V45, P1088 CAPLUS
(7) Kosir; J Surg Res 1997, V67, P98 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

ST **heparanase antibody** nucleic acid probe cancer

IT Primers (nucleic acid)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DNA; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT PCR (polymerase chain reaction)
(RT-PCR (reverse transcription-PCR); **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Lymphoma
(T-cell; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Carcinoma
Ovary, neoplasm
(adenocarcinoma; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Diagnosis
(agents; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Proteins, general, processes
RL: REM (Removal or disposal); PROC (Process)
(body fluid; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease,

diabetes and inflammation)
IT Mammary gland
(carcinoma, metastasis; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)
IT Bladder
Mammary gland
Prostate gland
(carcinoma; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)
IT Uterus, neoplasm
(cervix, metastasis; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)
IT Uterus, neoplasm
(cervix, squamous cell carcinoma; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)
IT Uterus, neoplasm
(cervix; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)
IT Intestine, neoplasm
(colon, adenocarcinoma; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)
IT Intestine, neoplasm
(colon, carcinoma, metastasis; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)
IT Intestine, neoplasm
(colon; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)
IT Kidney, disease
(diabetic nephropathy; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)
IT Pleura
(effusion; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)
IT Animal cell
Animal tissue
Autoimmune disease
Blood plasma
Body fluid
Carcinoma
DNA sequences
Diabetes mellitus
Drug delivery systems
Drug targeting
Drugs
Electrophoresis
Hybridoma
Inflammation
Intestine, neoplasm
Kidney, disease
Labels
Leukemia
Liver, neoplasm
Lymphoma
Melanoma
Multiple myeloma
Neoplasm
Ovary, neoplasm
PCR (polymerase chain reaction)
Pancreas, neoplasm
Protein sequences
Saliva
Sepsis
Skin, neoplasm
Stomach, neoplasm
Urine
Uterus, neoplasm
(**heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)
IT Nucleoside triphosphates
mRNA
RL: BSU (Biological study, unclassified); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)
IT Antisense DNA
Antisense RNA
Oligonucleotides
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)
IT **Antibodies**
Probes (nucleic acid)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)
IT Liver, neoplasm
(hepatoma; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)
IT Gene, animal
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hpa; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)
IT Diabetes mellitus
(insulin-dependent, microalbuminuric; **heparanase**-specific

antibodies and nucleic acid probes for [redacted]nosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Diabetes mellitus
(insulin-dependent, normoalbuminuric; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Mesothelium
(mesothelioma; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Intestine, neoplasm
Liver, neoplasm
Neoplasm
Ovary, neoplasm
Pancreas, neoplasm
Prostate gland
Skin, neoplasm
Stomach, neoplasm
Uterus, neoplasm
(metastasis; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Antigens
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(moiety; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT **Antibodies**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Bladder
Mammary gland
(neoplasm, metastasis; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Bladder
Mammary gland
Prostate gland
(neoplasm; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Kidney, disease
(nephritis, hemorrhagic; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Kidney, disease
(nephrotic syndrome; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT DNA
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(primer; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Nucleic acids
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(probe; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Separation
(size; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Neoplasm
(solid; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Drug delivery systems
(solns.; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Carcinoma
(squamous cell; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Carcinoma
(teratocarcinoma; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT Hematopoietic precursor cell
(tumors; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT 221113-49-1, Heparanase (human gene hpa)
RL: PRP (Properties)
(amino acid sequence; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT 89800-66-8, **Heparanase**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT 249927-19-3 249927-20-6 249927-21-7 249927-22-8
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT 250215-44-2
RL: PRP (Properties)
(nucleotide sequence; **heparanase**-specific **antibodies** and nucleic acid probes for diagnosis and therapy of cancer, renal disease, diabetes and inflammation)

IT 9012-90-2, DNA polymerase
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thermostable; **heparanase**-specific **antibodies** and

nucleic acid probes for diagnosis and py of cancer, renal disease, diabetes and inflammation)

L4 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:566196 CAPLUS
DOCUMENT NUMBER: 131:181667
TITLE: Human platelet heparanase polypeptides, polynucleotide molecules that encode them, and methods for the identification of compounds that alter heparanase activity
INVENTOR(S): Heinrikson, Robert L.; Fairbanks, Michael B.; Mildner, Ana M.
PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9943830	A2	19990902	WO 1999-US1489	19990218
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9927591	A1	19990915	AU 1999-27591	19990218
EP 1060252	A2	20001220	EP 1999-908073	19990218
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1998-75706 P 19980224
US 1998-79401 P 19980326
WO 1999-US1489 W 19990218

AB The present invention provides isolated human heparanase polypeptides, and the isolated polynucleotide mols. that encode them, as well as vectors and host cells comprising such polynucleotide mols. Heparanase is purified from human platelets (20.mu.g from 2000 mL platelet-rich plasma) by heparin-Sepharose chromatog., size exclusion chromatog. on Superdex-75, and heparin HiTrap column chromatog. The heparanase transcript encodes a 530-amino acid residue prepro enzyme which is processed to form 8-kDa and 56-kDa subunits. The invention also provides a method for the identification of an agent that alters heparanase activity.

IT **Antibodies**
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(human platelet **heparanase** polypeptides, polynucleotide mols. that encode them, and methods for the identification of compds. that alter heparanase activity)

L4 ANSWER 14 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:511264 CAPLUS
DOCUMENT NUMBER: 131:141481
TITLE: Human heparanase obtained from SV-40-transformed cell line, its cDNA and amino acid sequences, recombinant expression and its biological, diagnostic and therapeutic uses
INVENTOR(S): Nakajima, Motowo; Toyoshima, Minako
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9940207	A1	19990812	WO 1999-EP777	19990205
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9928319	A1	19990823	AU 1999-28319	19990205
EP 1054980	A1	20001129	EP 1999-908854	19990205
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: GB 1998-2725 A 19980209
WO 1999-EP777 W 19990205

AB This invention presents a polynucleotide (cDNA mol.) encoding human heparanase, which was obtained from the SV-40-transformed fibroblast cell line ATCC CCL 75.1. The invention also provides a hybrid vector contg. the human heparanase polynucleotide, and a host cell transformed with the vector. The invention further provides an antibody that specifically recognizes and binds the **heparanase**, and use of this **antibody** in treatment of diseases assocd. with abnormal expression or activity of heparanase. Still further, the invention presents the therapeutic, diagnostic and biol. uses of human heparanase including the use of heparanase to identify agonist or antagonists of heparanase. Finally, the invention presents an oligonucleotide capable of specifically hybridizing with the human heparanase polynucleotide, and use of the human heparanase polynucleotide in gene therapy. The cDNA sequence encoding human heparanase, as well as the amino acid sequences encoding the prepro and mature forms of heparanase are claimed. The heparanase is an endoglucuronidase capable of specifically degrading heparan sulfate into 6 to 20 kDa fragments.

REFERENCE COUNT: 10
REFERENCE(S): (1) Christopher, R; WO 9633726 A 1996 CAPLUS
(2) Goshen; Molecular Human Reproduction 1996, V2(9), P679 CAPLUS
(3) Hadassah Med Org; WO 9102977 A 1991 CAPLUS

(4) Hamdorf, B; WO 992[redacted] 1999 CAPLUS
(6) Hoogwerf, A; WO 9504158 A 1995 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB This invention presents a polynucleotide (cDNA mol.) encoding human heparanase, which was obtained from the SV-40-transformed fibroblast cell line ATCC CCL 75.1. The invention also provides a hybrid vector contg. the human heparanase polynucleotide, and a host cell transformed with the vector. The invention further provides an antibody that specifically recognizes and binds the **heparanase**, and use of this **antibody** in treatment of diseases assocd. with abnormal expression or activity of heparanase. Still further, the invention presents the therapeutic, diagnostic and biol. uses of human heparanase including the use of heparanase to identify agonist or antagonists of heparanase. Finally, the invention presents an oligonucleotide capable of specifically hybridizing with the human heparanase polynucleotide, and use of the human heparanase polynucleotide in gene therapy. The cDNA sequence encoding human heparanase, as well as the amino acid sequences encoding the prepro and mature forms of heparanase are claimed. The heparanase is an endoglucuronidase capable of specifically degrading heparan sulfate into 6 to 20 kDa fragments.

IT **Antibodies**
RL: ARG (Analytical reagent use); BPR (Biological process); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(anti-human **heparanase**, used in treatment of diseases; human heparanase obtained from SV-40-transformed cell line, its cDNA and amino acid sequences, recombinant expression and its biol., diagnostic and therapeutic uses)

L4 ANSWER 15 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:303252 CAPLUS
DOCUMENT NUMBER: 130:322335
TITLE: Isolated nucleic acid molecule encoding mammalian endoglucuronidase and its therapeutic uses for enhancing wound healing and related disorders
INVENTOR(S): Freeman, Craig Geoffrey; Hulett, Mark Darren; Parish, Christopher Richard; Hamdorf, Brenton James
PATENT ASSIGNEE(S): The Australian National University, Australia
SOURCE: PCT Int. Appl., 112 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9921975	A1	19990506	WO 1998-AU898	19981028
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9910109	A1	19990517	AU 1999-10109	19981028
ZA 9809824	A	19990624	ZA 1998-9824	19981028
BR 9813296	A	20000822	BR 1998-13296	19981028
EP 1032656	A1	20000906	EP 1998-952409	19981028
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6242238	B1	20010605	US 1998-181336	19981028

PRIORITY APPLN. INFO.:
AU 1997-62 A 19971028
AU 1997-812 A 19971209
US 1998-181336 A 19981028
WO 1998-AU898 W 19981028

AB The present invention relates to isolated or recombinant mammalian endoglucuronidase enzymes, polypeptides and peptides, in particular human, murine and rat heparanases, and genetic sequences encoding the enzymes. The full-length cDNA sequence of the human heparanase enzyme contains an open reading frame encoding a 543-amino acid protein. Also included are uses in the detn. and characterization of chem. compds., proteins, polypeptides, small mols. and macromols. capable of inhibiting metastasis, angiogenesis, angioplasty-induced restenosis, atherosclerosis, inflammation, promote wound healing and otherwise modulate physiol. processes involving heparanase cleavage of heparan sulfate. The invention further relates to a method of altering, modifying or otherwise modulating the level of expression of mammalian heparanase in a cell. A further aspect of the invention relates to immunoreactive mols. capable of binding to and/or inhibiting mammalian **heparanase**, in particular monoclonal **antibodies**. A still further aspect of the invention contemplates the use of heparanase as an agent to promote the processes of wound healing.

REFERENCE COUNT: 2
REFERENCE(S): (1) Turnbull, J; Biochem J V265, P715 CAPLUS
(2) Turnbull, J; Biochem J 1991, V273, P553 CAPLUS

AB The present invention relates to isolated or recombinant mammalian endoglucuronidase enzymes, polypeptides and peptides, in particular human, murine and rat heparanases, and genetic sequences encoding the enzymes. The full-length cDNA sequence of the human heparanase enzyme contains an open reading frame encoding a 543-amino acid protein. Also included are uses in the detn. and characterization of chem. compds., proteins, polypeptides, small mols. and macromols. capable of inhibiting metastasis, angiogenesis, angioplasty-induced restenosis, atherosclerosis, inflammation, promote wound healing and otherwise modulate physiol. processes involving heparanase cleavage of heparan sulfate. The invention further relates to a method of altering, modifying or otherwise modulating the level of expression of mammalian heparanase in a cell. A further aspect of the invention relates to immunoreactive mols. capable of binding to and/or inhibiting mammalian **heparanase**, in particular monoclonal **antibodies**. A still further aspect of the invention contemplates the use of heparanase as an agent to promote the processes of wound healing.

L4 ANSWER 16 OF 23 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999386667 MEDLINE
DOCUMENT NUMBER: 99386667 PubMed ID: 10455023
TITLE: Evidence that platelet and tumour heparanases are similar enzymes.
AUTHOR: Freeman C; Browne A M; Parish C R
CORPORATE SOURCE: Division of Immunology and Cell Biology, John Curtin School of Medical Research, Australian National University,

Canberra, ACT, 2601, Austral[redacted]Craig.Freeman@anu.edu.au
SOURCE: BIOCHEMICAL JOURNAL, (1999 Sep 1) 342 (Pt 2) 361-8.
Journal code: 9YO; 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991101

AB In order to enter tissues, blood-borne metastatic tumour cells and leucocytes need to extravasate through the vascular basal lamina (BL), a process which involves a battery of degradative enzymes. A key degradative enzyme is the endoglycosidase heparanase, which cleaves heparan sulphate (HS), an important structural component of the vascular BL. Previously, tumour-derived heparanase activity (which has been shown to be related to the metastatic potential of murine and human melanoma cell lines) was reported to cleave HS and be inhibited by heparin, as distinct from human platelet heparanase, which cleaved both substrates [Nakajima, Irimura and Nicolson (1988) J. Cell Biochem. 36, 157-167]. We recently reported the purification of human platelet heparanase and showed that the enzyme is a 50-kDa endoglucuronidase [Freeman and Parish (1998) Biochem. J. 330, 1341-1350]. We now report the purification and characterization of heparanase activity from highly metastatic rat 13762 MAT mammary adenocarcinoma and human HCT 116 colonic carcinoma cells and from rat liver using essentially the same procedure that was reported for purification of the human platelet enzyme. The rat 13762 MAT tumour enzyme, which has a native M(r) of 45 kDa when analysed by gel-filtration chromatography and by SDS/PAGE, was observed to be an endoglucuronidase that degraded heparin and HS to fragments of the same sizes as the human platelet enzyme does. N-deglycosylation of both the human platelet and rat 13762 MAT tumour enzymes gave, in each case, a 41-kDa band by SDS/PAGE analysis, demonstrating that the observed difference in M(r) between the platelet and tumour enzymes may have been due largely to differences in the relative amounts of N-glycosylation. Two peptides were isolated following Endoproteinase Lys-C digestion of both the human platelet and rat 13762 MAT tumour heparanases and were shown to be highly similar. Both the rat liver and human colonic carcinoma heparanases also degraded both heparin and HS to fragments of the same sizes as the human platelet enzyme does. Western-blot analysis of an SDS/PAGE gel using **antibodies** raised against human platelet **heparanase** demonstrated that human platelet, human tumour and rat tumour heparanases were immunochemically cross-reactive. In conclusion, because of the similarities in their sizes, substrate specificities, peptide sequences and immunoreactivities, we propose that heparanase activities present in human platelets, rat liver and in rat and human tumour cells are, in fact, mediated by a similar enzyme.

AB . . . HS to fragments of the same sizes as the human platelet enzyme does. Western-blot analysis of an SDS/PAGE gel using **antibodies** raised against human platelet **heparanase** demonstrated that human platelet, human tumour and rat tumour heparanases were immunochemically cross-reactive. In conclusion, because of the similarities in. . .

L4 ANSWER 17 OF 23 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1999108041 MEDLINE
DOCUMENT NUMBER: 99108041 PubMed ID: 9889056
TITLE: Degradation of basement membrane by prostate tumor heparanase.
AUTHOR: Kosir M A; Wang W; Zukowski K L; Tromp G; Barber J
CORPORATE SOURCE: Department of Surgery, Wayne State University School of Medicine, Detroit, Michigan, 48201, USA..
KOSIR.MARY_ANN@DETROIT.VA.GOV
SOURCE: JOURNAL OF SURGICAL RESEARCH, (1999 Jan) 81 (1) 42-7.
Journal code: K7B; 0376340. ISSN: 0022-4804.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990311
Last Updated on STN: 19990311
Entered Medline: 19990223

AB BACKGROUND: The degradation of basement membrane (BM) by cancer is an important event that characterizes invasive biological behavior. A component of BM is heparan sulfate proteoglycan (HSPG). The glycanase(s) that degrade HSPG in BM are not yet isolated. We recently identified HSPG-degrading activity (PC-3M heparanase) in the conditioned media (CM) of malignant prostate carcinoma cells (PC-3M and LNCaP C4-2). **Antibodies** (Abs) to a recently isolated **heparanase** from human platelets (CTAP-III), cross-react with PC-3M heparanase although they differ in size; under reduced conditions PC-3M heparanase is 60 kDa whereas CTAP-III is 10 kDa by polyacrylamide gel electrophoresis. PC-3M heparanase therefore shares homology with CTAP-III. The purpose of this study was to test the inhibition of PC-3M heparanase by Abs specific to the N- and C-terminals of CTAP-III. MATERIALS AND METHODS: CM from PC-3M and LNCaP C4-2 cells were tested for heparanase activity. Each reaction contained substrate as [3H]glucosamine-labeled HSPG (>50 kDa) from the BM of the EHS tumor, CM from PC-3M or LNCaP C4-2 cells, and inhibitor or buffer (negative control). Protease inhibitors were present throughout. After incubation for 3-20 h at 37 degreesC and pH 5.8, the reaction was stopped with 0.2% SDS. Each reaction mixture was centrifuged in an Ultrafree-MC 30,000 NMWL filter unit (Millipore) and radioactivity in the filtrate counted by scintillation counting. Results. For both cell lines, there was a linear relationship between the amount (microgram) of CM and degradation of HSPG. Degradation was inhibited by 54.1% (mean) using carrageenan lambda (10 microgram/ml), a nonspecific glycanase inhibitor ($P < 0.05$ by ANOVA). Ab to the N-terminus of CTAP-III (anti-Hep A) reduced degradation by 10-50% (mean 31.1%) and to the C-terminus (anti-Hep C) by 38.8-64.3% (mean 51.1%) ($P < 0.003$ by ANOVA). CONCLUSIONS: The degradation of HSPG by malignant prostate cancer cell lines is inhibited by both a nonspecific glycanase inhibitor, and specific Abs to a homologous platelet heparanase. Based upon molecular weight, PC-3M heparanase is different from platelet heparanase and degrades BM.

AB . . . recently identified HSPG-degrading activity (PC-3M heparanase) in the conditioned media (CM) of malignant prostate carcinoma cells (PC-3M and LNCaP C4-2). **Antibodies** (Abs) to a recently isolated **heparanase** from human platelets (CTAP-III), cross-react with PC-3M heparanase although they differ in size; under reduced conditions PC-3M heparanase is 60. . .

L4 ANSWER 18 OF 23 MEDLINE DUPLICATE 7

ACCESSION NUMBER: 1998008076 MEDLINE
DOCUMENT NUMBER: 98008076 PubMed ID: 9581574
TITLE: Major co-localization of the extracellular-matrix degradative enzymes heparanase and gelatinase in tertiary granules of human neutrophils.
AUTHOR: Mollinedo F; Nakajima M; Llorens A; Barbosa E; Callejo S; Gajate C; Fabra A
CORPORATE SOURCE: Laboratory of Signal Transduction and Leucocyte Biology, Instituto de Biologia y Genetica Molecular, Facultad de Medicina, Consejo Superior de Investigaciones Cientificas-Universidad de Valladolid, C/ Ramon y Cajal, E-47005 Valladolid, Spain.
SOURCE: BIOCHEMICAL JOURNAL, (1997 Nov 1) 327 (Pt 3) 917-23. Journal code: 9YO; 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980529
Last Updated on STN: 20000303
Entered Medline: 19980520

AB The expression of cell-surface adhesion proteins and the release of extracellular-matrix degradative enzymes constitute crucial processes for the attachment of neutrophils to the endothelium and for the subsequent extravasation of these cells through the endothelial layer. We have analysed in resting human neutrophils the subcellular localization of heparanase, a heparan-sulphate-degrading endoglycosidase that can degrade basement-membrane components, thereby facilitating neutrophil passage into the tissue during an inflammatory reaction. By subcellular fractionation of postnuclear supernatants from resting human neutrophils on continuous sucrose gradients, we have found that heparanase activity was mainly located in gelatinase-containing tertiary granules. Using a specific **antibody**, the 96-kDa **heparanase** protein was further located in the gelatinase-rich subcellular fractions. Following immunoblotting and immunoprecipitation analysis in the distinct subcellular fractions, we also found co-localization of heparanase and Mo1 (CD11b/CD18), a leucocyte integrin involved in the attachment of neutrophils to the endothelium, in the fractions enriched in gelatinase-containing tertiary granules. Treatment of human neutrophils with tumour necrosis factor or granulocyte/macrophage colony-stimulating factor induced an increase in the CD11b/CD18 cell-surface expression, as well as the release of both gelatinase (matrix metalloproteinase-9) and heparanase, but not of other granule markers, indicating a major co-localization of gelatinase, heparanase and CD11b/CD18 in the same organelle. Furthermore, confocal laser scanning microscopy using specific **antibodies** against gelatinase and **heparanase** revealed a major co-localization of both enzymes in intracellular cytoplasmic granules. The major localization of heparanase and CD11b/CD18 in the gelatinase-containing tertiary granule supports the notion that mobilization of this organelle can regulate extravasation of human neutrophils.

AB . . . on continuous sucrose gradients, we have found that heparanase activity was mainly located in gelatinase-containing tertiary granules. Using a specific **antibody**, the 96-kDa **heparanase** protein was further located in the gelatinase-rich subcellular fractions. Following immunoblotting and immunoprecipitation analysis in the distinct subcellular fractions, we. . . indicating a major co-localization of gelatinase, heparanase and CD11b/CD18 in the same organelle. Furthermore, confocal laser scanning microscopy using specific **antibodies** against gelatinase and **heparanase** revealed a major co-localization of both enzymes in intracellular cytoplasmic granules. The major localization of heparanase and CD11b/CD18 in the. . .

L4 ANSWER 19 OF 23 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 97223306 MEDLINE
DOCUMENT NUMBER: 97223306 PubMed ID: 9070190
TITLE: Human prostate carcinoma cells produce extracellular heparanase.
AUTHOR: Kosir M A; Quinn C C; Zukowski K L; Grignon D J; Ledbetter S
CORPORATE SOURCE: Surgical Service, VA Medical Center, Detroit, Michigan 48201, USA.
SOURCE: JOURNAL OF SURGICAL RESEARCH, (1997 Jan) 67 (1) 98-105. Journal code: K7B; 0376340. ISSN: 0022-4804.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970414
Last Updated on STN: 19970414
Entered Medline: 19970403

AB The degradation of heparan sulfate proteoglycan (HSPG) in basement membranes (BM) has been previously suggested to be accomplished by an endoglycosidase activity called heparanase which has not been isolated outside of platelets. HSPG degradation by heparanase has been associated with tumor cell invasion, angiogenesis, and growth factor function. In this study, we identify heparanase activity biochemically and immunologically in malignant human prostate carcinoma cells (PC-3M), linking platelet heparanase probes with the tumor heparanase activity observed. Concentrated conditioned medium from PC-3M cells was analyzed by a heparin-Sepharose affinity column. Three peaks eluted with 0.15, 0.35, and 0.5 M NaCl. Each peak was analyzed by incubation with 3H-labeled heparin as well as [3H]HSPG from EHS tumor BM. The 0.5 M peak material degraded [3H]-heparin by 17.2%, with little additional degradation by the other peaks in comparison to the conditioned medium from which they were obtained. Likewise, the same amount of the 0.5 M peak accounted for the majority of degradation (30.8%) of 3H-labeled HSPG. Interestingly, for the same amount of 0.5 M peak material, significantly more HSPG was degraded than heparin under the same conditions. In addition, carrageenan-lambda, an inhibitor of glycanase, completely inhibited the degradation of heparin and heparan sulfate proteoglycan by the 0.5 M peak. Using antibody to the N-terminus domain of platelet heparanase, a 60-kDa protein was identified by immunoblot in 0.5 M peak material. Additionally, immunohistochemical staining of human prostate carcinoma specimens showed granular staining at or near the cell membrane and near the luminal surface using antibody to the N-terminus and C-terminus domains of platelet heparanase. In summary, human prostate carcinoma cells show heparanase activity in conditioned medium that degrades heparin and BM HSPG and is detected by **antibody** to platelet **heparanase**. In addition, the membrane-associated staining in tissue sections of prostate cancer strongly correlates with the biochemical and immunological detection in

conditioned medium of human PC-3M cells.

AB . . . human prostate carcinoma cells show heparanase activity in conditioned medium that degrades heparin and BM HSPG and is detected by **antibody** to platelet **heparanase**. In addition, the membrane-associated staining in tissue sections of prostate cancer strongly correlates with the biochemical and immunological detection in. . .

L4 ANSWER 20 OF 23 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 94148528 MEDLINE
DOCUMENT NUMBER: 94148528 PubMed ID: 8314313
TITLE: Immunoselection of GRP94/endoplasmin from a KNRK cell-specific lambda gt11 library using **antibodies** directed against a putative **heparanase** amino-terminal peptide.
AUTHOR: De Vouge M W; Yamazaki A; Bennett S A; Chen J H; Shwed P S; Couture C; Birnboim H C
CORPORATE SOURCE: Ottawa Regional Cancer Centre, Ontario, Canada.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1994 Jan 15) 56 (2) 286-94.
Journal code: GQU; 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-S69315; GENBANK-S69316
ENTRY MONTH: 199403
ENTRY DATE: Entered STN: 19940330
Last Updated on STN: 19960129
Entered Medline: 19940322

AB Induction of an invasive phenotype by metastatic tumour cells results in part from inappropriate expression of extracellular matrix-degrading enzymes normally involved in embryonic morphogenesis, tissue remodelling, angiogenesis and wound healing. Such enzymes include endoglycosidases that degrade heparan sulfate (HS) in endothelial basement membrane, as well as better characterized proteases. Heparanase, an endo-beta-D-glucuronidase initially detected in B16 melanoma cells, has been described as a M(r) 96,000 glycoprotein with pI of 5.2, and has been immunolocalized to the cell surface and cytoplasm. We have utilized a polyacrylamide-gel-based HS degradation assay to demonstrate that KNRK, a rat kidney fibroblast cell line transformed by v-K-ras, exhibits HS-degrading activity similar to that of B16F10 mouse melanoma cells. To immunoselect heparanase-expressing clones from a KNRK-cell-specific lambda gt11 cDNA library, we have also prepared a rabbit anti-serum directed against a putative amino-terminal peptide of B16F10 cellular heparanase. Lysogens from one clone expressed a beta-galactosidase fusion protein whose staining with peptide anti-serum was inhibited by competition with excess peptide. Dideoxy-mediated sequencing of the insert termini of this recombinant revealed that it represents a rat homologue of M(r) 94,000 glucose-regulated protein (GRP94/endoplasmin), a molecular chaperone that contains the exact amino-terminal sequence previously attributed to heparanase. Our results call into question the specificity of this peptide sequence, as well as previous immunolocalization studies of heparanase carried out using such anti-sera.

TI Immunoselection of GRP94/endoplasmin from a KNRK cell-specific lambda gt11 library using **antibodies** directed against a putative **heparanase** amino-terminal peptide.

L4 ANSWER 21 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:190176 CAPLUS
DOCUMENT NUMBER: 116:190176
TITLE: Antibodies, kits, and methods for immunochemical localization of heparanase in mouse and human melanomas, and characterization of melanoma heparanase
INVENTOR(S): Nicolson, Garth L.; Nakajima, Motowo; Jin, Li
PATENT ASSIGNEE(S): University of Texas System, USA
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9119197	A1	19911212	WO 1991-US3832	19910530
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
AU 9182317	A1	19911231	AU 1991-82317	19910530
AU 641269	B2	19930916		
EP 532695	A1	19930324	EP 1991-913555	19910530
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 05509403	T2	19931222	JP 1991-512410	19910530
PRIORITY APPLN. INFO.:			US 1990-530869	19900531
			WO 1991-US3832	19910530

AB **Antibodies** to a glycosaminoglycan endoglycosidase (esp. **heparanase**), as well as kits and methods employing the antibodies, are disclosed. **Antibodies** against an N-terminal **heparanase** peptide are produced. These antibodies are used for the detection of heparan sulfate endoglycosidase in human and murine tumors. Purifn. of melanoma heparanase is described. A hemocyanin-coupled heparanase-derived peptide was used as an immunogen for antibody prodn. Also described is prepn. and reactivity of various substrates (e.g. desulfated or desulfated and acetylated heparan sulfate) with melanoma heparanase. The anti-**heparanase** **antibodies** of the invention stained metastatic melanoma cells, but did not stain surrounding tissue.

AB **Antibodies** to a glycosaminoglycan endoglycosidase (esp. **heparanase**), as well as kits and methods employing the antibodies, are disclosed. **Antibodies** against an N-terminal **heparanase** peptide are produced. These antibodies are used for the detection of heparan sulfate endoglycosidase in human and murine tumors. Purifn. of melanoma heparanase is described. A hemocyanin-coupled heparanase-derived peptide was used as an immunogen for antibody prodn. Also described is prepn. and reactivity of various substrates (e.g. desulfated or desulfated and acetylated heparan sulfate) with melanoma heparanase. The anti-**heparanase** **antibodies** of the invention stained metastatic melanoma cells, but did not stain surrounding tissue.

ST glycosaminoglycan endoglycosidase antibody; **heparanase** melanoma **antibody**

IT Animal cell line
(B16-F10, **heparanase** purifn. from, **antibodies** for

melanoma localization in relation to)
IT Melanoma
(**heparanase** of, purifn. of and **antibodies** for localization of)
IT **Antibodies**
RL: ANST (Analytical study)
(to **heparanase**, melanoma localization in relation to)
IT Hemocyanins
Proteins, specific or class
RL: ANST (Analytical study)
(conjugates, with **heparanase** peptide, for anti-**heparanase antibody** prodn.)
IT Melanoma
(metastatic, anti-**heparanase antibodies** staining of)
IT 89800-66-8, **Heparanase** 140879-15-8
RL: ANST (Analytical study)
(**antibodies** to and immunochem. detection of, melanoma localization in relation to)
IT 139775-54-5 139878-83-4
RL: ANST (Analytical study)
(for anti-**heparanase antibody** prodn.)

L4 ANSWER 22 OF 23 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 90277246 MEDLINE
DOCUMENT NUMBER: 90277246 PubMed ID: 2351486
TITLE: Immunochemical localization of heparanase in mouse and human melanomas.
AUTHOR: Jin L; Nakajima M; Nicolson G L
CORPORATE SOURCE: Department of Tumor Biology, University of Texas M.D. Anderson Cancer Center, Houston 77030.
CONTRACT NUMBER: P30-CA16672 (NCI)
R01-CA41524 (NCI)
R35-CA44352 (NCI)
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1990 Jun 15) 45 (6) 1088-95.
Journal code: GQU; 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199007
ENTRY DATE: Entered STN: 19900824
Last Updated on STN: 19970203
Entered Medline: 19900719
AB Heparanase, an endo-beta-D-glucuronidase, has been associated with melanoma metastasis. Polyclonal antibodies directed against the murine N-terminal heparanase peptide detected a Mr approximately 97,000 protein on SDS-PAGE of mouse melanoma and human melanoma cell lysates. In an indirect immunocytochemical study, human A375-SM and mouse B 16-BL6 melanoma cells were stained with the anti-**heparanase antibodies**. **Heparanase** antigen was localized in the cytoplasm of permeabilized melanoma cells as well as at the cell surface of unpermeabilized cells. Immunohistochemical staining of frozen sections from syngeneic mouse lungs containing micrometastases of B16-BL6 melanoma demonstrated heparanase localized in metastatic melanoma cells. Similar studies using frozen sections of malignant melanomas resected from patients indicated that heparanase is localized in invading melanoma cells. Our studies suggest that (a) the N-terminus of the heparanase molecule in mouse and human is antigenically related; (b) heparanase antigens are localized at the cell surface and in the cytoplasm of metastatic human and mouse melanoma cells; and (c) heparanase antigens are enriched in invasive and metastatic murine and human melanomas in vivo.
AB . . . melanoma cell lysates. In an indirect immunocytochemical study, human A375-SM and mouse B 16-BL6 melanoma cells were stained with the anti-**heparanase antibodies**. **Heparanase** antigen was localized in the cytoplasm of permeabilized melanoma cells as well as at the cell surface of unpermeabilized cells.. . .

L4 ANSWER 23 OF 23 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 87109488 MEDLINE
DOCUMENT NUMBER: 87109488 PubMed ID: 2433294
TITLE: Soluble antigen induces T lymphocytes to secrete an endoglycosidase that degrades the heparan sulfate moiety of subendothelial extracellular matrix.
AUTHOR: Fridman R; Lider O; Naparstek Y; Fuks Z; Vlodavsky I; Cohen I R
CONTRACT NUMBER: CA 30289 (NCI)
NS 1868 (NINDS)
SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, (1987 Jan) 130 (1) 85-92.
Journal code: HNB; 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198703
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 19970203
Entered Medline: 19870311
AB The antigen-mediated induction of heparanase, an endoglycosidase capable of degrading heparan sulfate from the subendothelial extracellular matrix (ECM), was investigated in a rat T lymphocyte cell line reactive against the basic protein (BP) of myelin. We found that nonactivated T lymphocytes could be induced to express heparanase activity following exposure to soluble but not to ECM-bound BP. The induction of heparanase was immunologically specific and independent of the presence of syngeneic or allogeneic antigen presenting cells (APC). However, anti-IA **antibodies** inhibited **heparanase** expression. Soluble BP induced secretion of heparanase into the culture medium within minutes, despite inhibition of protein synthesis. Cell lysates of T lymphocytes contained heparanase activity. Thus, T lymphocytes secrete a preformed heparanase following exposure to specific antigen.
AB . . . of heparanase was immunologically specific and independent of the presence of syngeneic or allogeneic antigen presenting cells (APC). However, anti-IA **antibodies** inhibited **heparanase** expression. Soluble BP induced secretion of heparanase into the culture medium within minutes, despite inhibition of protein synthesis. Cell lysates. . .

=> end
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☐ 1. Document ID: US 20010006630 A1

L1: Entry 1 of 11 File: PGPB Jul 5, 2001

PGPUB-DOCUMENT-NUMBER: 20010006630
PGPUB-FILING-TYPE: new-utility
DOCUMENT-IDENTIFIER: US 20010006630 A1

TITLE: INTRODUCING A BIOLOGICAL MATERIAL INTO A PATIENT

PUBLICATION-DATE: July 5, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
YACOBY-ZEEVI, ORON	MEITAR		IL	

US-CL-CURRENT: 424/93.2; 424/94.64, 424/94.67, 435/325

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6242238 B1

L1: Entry 2 of 11 File: USPT Jun 5, 2001

US-PAT-NO: 6242238
DOCUMENT-IDENTIFIER: US 6242238 B1

TITLE: Isolated nucleic acid molecule encoding mammalian endoglucuronidase and uses therefor

DATE-ISSUED: June 5, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Freeman; Craig Geoffrey	Rivett	N/A	N/A	AUX
Hulett; Mark Darren	Cook	N/A	N/A	AUX
Parish; Christopher Richard	Campbell	N/A	N/A	AUX
Hamdorf; Brenton James	Swinger Hill	N/A	N/A	AUX

US-CL-CURRENT: 435/200; 435/252.3, 435/320.1, 536/23.1, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: US 6190875 B1

L1: Entry 3 of 11 File: USPT Feb 20, 2001

US-PAT-NO: 6190875
DOCUMENT-IDENTIFIER: US 6190875 B1

TITLE: Method of screening for potential anti-metastatic and anti-inflammatory agents using mammalian heparanase as a probe

DATE-ISSUED: February 20, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ben-Artzi; Hanna	Zion	N/A	N/A	ILX
Ayal-Hershkovitz; Maty	Herzliya	N/A	N/A	ILX
Vlodavsky; Israel	Zion	N/A	N/A	ILX
Pecker; Iris	Zion	N/A	N/A	ILX
Peleg; Yoav	Rehovot	N/A	N/A	ILX
Miron; Daphna	Rehovot	N/A	N/A	ILX

US-CL-CURRENT: 435/18; 435/201

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Drawi Desc | Image

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☐ 4. Document ID: US 6177545 B1

L1: Entry 4 of 11 File: USPT Jan 23, 2001

US-PAT-NO: 6177545
DOCUMENT-IDENTIFIER: US 6177545 B1

TITLE: Heparanase specific molecular probes and their use in research and medical applications

DATE-ISSUED: January 23, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pecker; Iris	Rishon Le Zion	N/A	N/A	ILX
Vlodavsky; Israel	Mevaseret Zion	N/A	N/A	ILX
Friedman; Yael	Jerusalem	N/A	N/A	ILX
Perets; Tuvia	Ramat Gan	N/A	N/A	ILX

US-CL-CURRENT: 530/387.3; 530/388.1, 530/388.2, 530/388.26, 530/388.85, 530/389.1, 530/413

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Drawi Desc | Image

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☐ 5. Document ID: US 5968822 A

L1: Entry 5 of 11 File: USPT Oct 19, 1999

US-PAT-NO: 5968822
DOCUMENT-IDENTIFIER: US 5968822 A

TITLE: Polynucleotide encoding a polypeptide having heparanase activity and expression of same in transduced cells

DATE-ISSUED: October 19, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pecker; Iris	Rishon le Zion 75203	N/A	N/A	ILX
Vlodavsky; Israel	Mevaseret Zion 90805	N/A	N/A	ILX
Feinstein; Elena	Rehovot 76214	N/A	N/A	ILX

US-CL-CURRENT: 435/325; 435/200, 435/252.3, 435/320.1, 536/23.1, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 6. Document ID: US 5362641 A

L1: Entry 6 of 11 File: USPT Nov 8, 1994

US-PAT-NO: 5362641
DOCUMENT-IDENTIFIER: US 5362641 A

TITLE: Heparanase derived from human Sk-Hep-1 cell line

DATE-ISSUED: November 8, 1994

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fuks; Zvi	New York	NY	N/A	N/A
Vlodavsky; Israel	Gilo	N/A	N/A	ILX

US-CL-CURRENT: 435/209; 435/195, 435/200, 435/201

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 7. Document ID: AU 200028786 A, WO 200052178 A1

L1: Entry 7 of 11 File: DWPI Sep 21, 2000

DERWENT-ACC-NO: 2000-579289
DERWENT-WEEK: 200065

TITLE: New polynucleotides encoding a polypeptide having heparanase activity, useful in wound healing and in gene therapy, particularly in treating tumor, inflammation, autoimmunity, neurodegenerative diseases

INVENTOR: FEINSTEIN, E; PECKER, I ; VLODAVSKY, I

PRIORITY-DATA: 1999US-0258892 (March 1, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 200028786 A	September 21, 2000	N/A	000	C12N015/56
WO 200052178 A1	September 8, 2000	E	152	C12N015/56

INT-CL (IPC): C12N 1/21; C12N 9/24; C12N 15/11; C12N 15/56; C12N 15/63

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 8. Document ID: NO 200102190 A, WO 200025817 A1, AU 200013314 A

L1: Entry 8 of 11 File: DWPI Jun 12, 2001

DERWENT-ACC-NO: 2000-399323
DERWENT-WEEK: 200141

TITLE: New monoclonal antibody comprising heparanase neutralizing activity, useful for treating a condition associated with heparanase expression e.g. preventing angiogenesis

INVENTOR: AYAL-HERSHKOVITZ, M; FRIEDMAN, Y ; MIRON, D ; PECKER, I ; PERETZ, T ; SHLOMI, Y ; VLODAVSKY, I

PRIORITY-DATA: 1998US-0186200 (November 4, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
NO 200102190 A	June 12, 2001	N/A	000	A61K000/00
WO 200025817 A1	May 11, 2000	E	028	A61K039/395
AU 200013314 A	May 22, 2000	N/A	000	A61K039/395

INT-CL (IPC): A61K 0/00; A61K 38/47; A61K 39/395; C07K 16/40

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 9. Document ID: EP 1054980 A1, WO 9940207 A1, AU 9928319 A

L1: Entry 9 of 11 File: DWPI Nov 29, 2000

DERWENT-ACC-NO: 1999-494300
DERWENT-WEEK: 200063

TITLE: New heparanase polypeptide useful for treating autoimmune diseases, skin diseases, cardiovascular diseases and nervous system diseases including Alzheimer's disease

INVENTOR: FUNAKUBO, M; NAKAJIMA, M ; TOYOSHIMA, M

PRIORITY-DATA: 1998GB-0002725 (February 9, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 1054980 A1	November 29, 2000	E	000	C12N015/56
WO 9940207 A1	August 12, 1999	E	040	C12N015/56
AU 9928319 A	August 23, 1999	N/A	000	C12N015/56

INT-CL (IPC): A61K 31/70; A61K 38/47; A61K 39/395; C07K 16/40; C12N 5/10; C12N 9/24; C12N 15/56; G01N 33/50; G01N 33/573 ; G01N 33/577

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 10. Document ID: AU 735116 B, WO 9911798 A1, AU 9891258 A, US 5968822 A, NO 9906228 A, EP 998569 A1, CZ 200000754 A3, HU 200002675 A2, CN 1272886 A

L1: Entry 10 of 11 File: DWPI Jun 28, 2001

DERWENT-ACC-NO: 1999-302255
DERWENT-WEEK: 200142

TITLE: New human polynucleotide useful for treating angiogenesis, restenosis, and inflammation

INVENTOR: FEINSTEIN, E; PECKER, I ; VLODAVSKY, I

PRIORITY-DATA: 1998US-0109386 (July 2, 1998), 1997US-0922170 (September 2, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 735116 B	June 28, 2001	N/A	000	C12N015/56
WO 9911798 A1	March 11, 1999	E	054	C12N015/56
AU 9891258 A	March 22, 1999	N/A	000	N/A
US 5968822 A	October 19, 1999	N/A	000	C12N015/56
NO 9906228 A	February 28, 2000	N/A	000	C12N000/00
EP 998569 A1	May 10, 2000	E	000	C12N015/56
CZ 200000754 A3	August 16, 2000	N/A	000	C12N015/56
HU 200002675 A2	December 28, 2000	N/A	000	C12N015/56
CN 1272886 A	November 8, 2000	N/A	000	C12N015/56

INT-CL (IPC): A61K 38/47; C12N 0/00; C12N 1/21; C12N 5/10; C12N 9/24; C12N 15/11; C12N 15/56; C12N 15/63

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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Terms	Documents
antibod$4 near heparanase	11

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Display Format: CIT Change Format

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☐ 11. Document ID: JP 3188691 B2, WO 9102977 A, AU 9063364 A, EP 487627 A1, JP 05504047 W, US 5362641 A, AU 654804 B, EP 487627 A4, EP 487627 B1, DE 69032406 E

L1: Entry 11 of 11 File: DWPI Jul 16, 2001

DERWENT-ACC-NO: 1991-087405
DERWENT-WEEK: 200142

TITLE: Purificn. of heparanaseon pressure-sensitive adhesive polymer contg. - by cation exchange resin chromatography and affinity absorbent purificn. of heparinase-contg. cell extract

INVENTOR: FUKS, Z; VLODAVSKY, I

PRIORITY-DATA: 1989US-0397554 (August 23, 1989), 1992US-0768900 (January 8, 1992)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 3188691 B2	July 16, 2001	N/A	020	C12N009/24
WO 9102977 A	March 7, 1991	N/A	000	N/A
AU 9063364 A	April 3, 1991	N/A	000	N/A
EP 487627 A1	June 3, 1992	E	000	G01N033/53
JP 05504047 W	July 1, 1993	N/A	000	C12N009/24
US 5362641 A	November 8, 1994	N/A	023	C12N009/26
AU 654804 B	November 24, 1994	N/A	000	C12N009/88
EP 487627 A4	March 3, 1993	N/A	000	N/A
EP 487627 B1	June 10, 1998	E	000	C12N009/24
DE 69032406 E	July 16, 1998	N/A	000	C12N009/24

INT-CL (IPC): A61K 37/48; A61K 37/54; A61K 37/56; A61K 38/46; A61P 17/02; C07K 1/14; C12N 9/14; C12N 9/24; C12N 9/26; C12N 9/42; C12N 9/88; C12Q 1/34; G01N 33/48; G01N 33/53; G01N 33/573

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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Terms	Documents
antibod$4 near heparanase	11

Display 10 Documents, starting with Document: 11

Display Format: CIT Change Format

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Search Results - Record(s) 1 through 10 of 11 returned.

☐ 1. Document ID: US 20010006630 A1

L1: Entry 1 of 11 File: PGPB Jul 5, 2001

DOCUMENT-IDENTIFIER: US 20010006630 A1
TITLE: INTRODUCING A BIOLOGICAL MATERIAL INTO A PATIENT

DRTX:
[0055] FIGS. 2a-b demonstrate that heparanase adheres to BMSCs and retains its activity. Cells that were incubated with heparanase were washed, collected and subjected to the (2a) DMB heparanase activity assay (1-6 represent six different experiments) and (2b) Western blot analysis using anti heparanase antibodies. T=Trypsin, 1E=1 mM EDTA, 2E=2 mM EDTA, Cb=control, purified heparanase from baculovirus, p60, Cc= control, purified heparanase from CHO cells, p45, kDa=kiloDaltons.

DRTX:
[0057] FIGS. 4a-c demonstrate that heparanase adheres to B16-F1 cells and retain its activity. Cells that were either transfected with the hpa cDNA ("transfected"), or incubated with heparanase ("adhered", +b22, or +b27), or not treated with heparanase (NT or -), were washed, collected and subjected to the DMB heparanase activity assay (4a), gel shift assay (4b), and Western blot analysis using anti heparanase antibodies (4c). Purified baculovirus heparanase p60 (b22, b27), or CHO heparanase p45 were used as controls (C).

DRTX:
[0058] FIGS. 5a-b demonstrate that heparanase binds to CHO-dhfr cell line, undergoes proteolytic cleavage and exhibits high heparanase activity. Cells that were incubated with heparanase were washed, collected and subjected to DMB activity assay (5a), and Western blot analysis using anti-heparanase antibodies (5b).

DETX:
[0126] Sputum viscosity and proteolytic activation of heparanase by sputum-borne proteases: 250 .mu.l of sputum samples, kept at 37.degree. C., were mixed in eppendorf tubes with either recombinant heparanase (p60), or with saline, or with a cocktail of protease inhibitors followed by the addition of heparanase, to make a total volume of 350 .mu.l. The samples were immediately transferred to 0.5 insulin syringes and tested for viscosity using a microviscosometer (Haake). The samples in the syringes were then incubated at 37.degree. C. and tested again for viscosity after 10, 50 and 120 minutes. Then, the samples were centrifuged for 10 minutes at 13,000 rpm and the supernatants were subjected to Western blot analysis, using several anti-heparanase antibodies (monoclonal Nos. 117 and 239, described in U.S. patent application Ser. No. 09/071,739, filed May 1, 1998).

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWMC | Draw Desc | Image

☐ 2. Document ID: US 6242238 B1

L1: Entry 2 of 11 File: USPT Jun 5, 2001

DOCUMENT-IDENTIFIER: US 6242238 B1
TITLE: Isolated nucleic acid molecule encoding mammalian endoglucuronidase and uses therefor

DEPR:
An ELISA assay was developed for assaying for anti-human heparanase antibodies. The assay involved immobilising human platelet heparanase (5 .mu.g/ml in PBS, 15 hr, 4.degree. C.), purified from human platelets as previously described, in 96 well plastic microplates (25 .mu.l/well). Non-specific binding sites were then blocked by the addition of 200 .mu.l/well of PBS containing 1% (w/v) bovine serum albumin (BSA) for 2 hr at 4.degree. C. Following three washes with 200 .mu.l/well of PBS/0/05% Tween 20 (PBST), 50 .mu.l/well of serial dilutions of the antisera in PBS/1% BSA were added and incubated for 2 hr at 4.degree. C. Following three washes with PBST, 50 .mu.L/well of horse radish peroxidase (HRP) coupled sheep anti-rabbit Ig was added in PBS/1% BSA for 1 hr at 4.degree. C., the plate again washed three times with PBST, and bound HRP measured by the addition of the colourometric HRP substrate 2,2'-azino-bis (3-ethylbenthiazoline-6-sulfonic acid diammonium salt (ABTS), colour development being measured at 405 nm on an ELISA plate reader after 30 minutes incubation at 37.degree. C.

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

☐ 3. Document ID: US 6190875 B1

L1: Entry 3 of 11 File: USPT Feb 20, 2001

DOCUMENT-IDENTIFIER: US 6190875 B1
TITLE: Method of screening for potential anti-metastatic and anti-inflammatory agents using mammalian heparanase as a probe

BSPR:
According to still further features in the described preferred embodiments the agent or agents include an anti-heparanase antibody.

DRPR:
One example include anti-heparanase antibodies. It is well known that by binding to the active site antibodies can be used to inhibit catalytic activity of an enzyme.

DRPR:
Anti-heparanase antibodies are described in length in U.S. patent application Ser. No. 09/071,739, which is incorporated by reference as if fully set forth herein.

CLPR:
6. The method of claim 1, wherein the agent is an anti-heparanase antibody.

CLPR:
18. The method of claim 14, wherein the agent is an anti-heparanase antibody.

CLPR:
38. The quantitative method of claim 26, wherein the agent is an anti-heparanase antibody.

CLPR:
56. The quantitative method of claim 44, wherein the agent is an anti-heparanase antibody.

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

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☐ 4. Document ID: US 6177545 B1

L1: Entry 4 of 11 File: USPT Jan 23, 2001

DOCUMENT-IDENTIFIER: US 6177545 B1
TITLE: Heparanase specific molecular probes and their use in research and medical applications

BSPR:
The present invention relates to heparanase specific molecular probes their use in research and medical applications. More particularly, the present invention relates to the use of heparanase specific molecular probes, such as anti-heparanase antibodies (both poly- and monoclonal) and heparanase gene (hpa) derived nucleic acids, including, but not limited to, PCR primers, antisense oligonucleotide probes, antisense RNA probes, DNA probes and the like for detection and monitoring of malignancies, metastasis and other non-malignant conditions, efficiency of therapeutic treatments, targeted drug delivery and therapy.

BSPR:
Heparanase activity could not be detected in normal stromal fibroblasts, mesothelial, endothelial and smooth muscle cells derived from non cancerous biopsies and effusions (12). These observations indicate that heparanase

expression may serve as a marker for tumor cells and in particular for those which are highly invasive or potentially invasive. If the same conclusion can be reached by immunostaining of tissue specimens, anti-heparanase antibodies may be applied for early detection and diagnosis of metastatic cell populations and micro-metastases.

BSPR:
Expression of heparanase by cells of the immune system: Heparanase activity correlates with the ability of activated cells of the immune system to leave the circulation and elicit both inflammatory and autoimmune responses. Interaction of platelets, granulocytes, T and B lymphocytes, macrophages and mast cells with the subendothelial ECM is associated with degradation of heparan sulfate (HS) by heparanase activity (7). The enzyme is released from intracellular compartments (e.g., lysosomes, specific granules) in response to various activation signals (e.g., thrombin, calcium ionophore, immune complexes, antigens, mitogens), suggesting its regulated involvement and presence in inflammatory sites and autoimmune lesions. Heparan sulfate degrading enzymes released by platelets and macrophages are likely to be present in atherosclerotic lesions (21). Hence, cDNA probes and anti-heparanase antibodies may be applied for detection and early diagnosis of these lesions.

BSPR:
On the basis of the examples described below, it appears that cDNA and RNA probes, PCR primers, and anti-heparanase antibodies (heparanase specific molecular probes) can be applied to detect the heparanase gene and protein and hence for early diagnosis of micrometastases, autoimmune lesions, renal failure and atherosclerotic lesions using biopsy specimens, plasma samples, and body fluids.

BSPR:
Collectively, it is evident that so far no one had succeeded in eliciting anti-heparanase antibodies.

BSPR:
According to still further features in the described preferred embodiments the elicitation is through in vivo or in vitro techniques, the antibody having been prepared by a process comprising the steps of (a) exposing cells capable of producing antibodies to the heparanase protein or the immonogenical part thereof and thereby generating antibody producing cells; (b) fusing the antibody producing cells with myeloma cells and thereby generating a plurality of hybridoma cells each producing monoclonal antibodies; and (c) screening the plurality of monoclonal antibodies to identify a monoclonal antibody which specifically binds heparanase.

BSPR:
According to still further features in the described preferred embodiments the detectable heparanase specific molecular probe is selected from the group consisting of a nucleic acid sequence hybridizable with heparanase encoding nucleic acid and an anti-heparanase antibody capable of specifically binding heparanase.

BSPR:
According to further features in preferred embodiments of the invention described below, there is provided a method of detecting heparanase protein in a body fluid of a patient comprising the steps of reacting the body fluid with an anti-heparanase antibody and monitoring the reaction.

BSPR:
According to still further features in the described preferred embodiments the anti-heparanase antibody is selected from the group consisting of a monoclonal antibody and a poly clonal antibody.

BSPR:
According to still further features in the described preferred embodiments

reacting the body fluid with the anti-heparanase antibody is effected in solution.

BSPR:
According to still further features in the described preferred embodiments reacting the body fluid with the anti-heparanase antibody is effected on a substrate capable of adsorbing proteins present in the body fluid.

BSPR:
According to further features in preferred embodiments of the invention described below, there is provided a method of detecting the presence, absence or level of heparanase protein in a biological sample comprising the steps of (a) extracting proteins from the biological sample, thereby obtaining a plurality of proteins; (b) size separating the proteins; (c) interacting the size separated proteins with an anti-heparanase antibody; and (d) detecting the presence, absence or level of the interacted anti-heparanase antibody.

BSPR:
According to still further features in the described preferred embodiments the anti-heparanase antibody is selected from the group consisting of a polyclonal antibody and a monoclonal antibody.

BSPR:
According to further features in preferred embodiments of the invention described below, there is provided a method of targeted drug delivery to a tissue of a patient, the tissue expressing heparanase, the method comprising the steps of providing a complex of a drug directly or indirectly linked to an anti-heparanase antibody and administering the complex to the patient.

BSPR:
According to further features in preferred embodiments of the invention described below, there is provided a method of treating a patient having a condition associated with heparanase expression comprising the step of administering an anti-heparanase antibody to the patient.

DRPR:
FIGS. 17a-b demonstrate Western blots of extracts of cells expressing various segments of heparanase as detected with polyclonal anti heparanase antibodies. 17a--antiserum from rabbit 7640, 17b--antiserum from rabbit 7644. Lane 1, E. coli BL21(DE3)pLysS cells transfected with pRSET, lane 2, E. coli BL21(DE3)pLysS cells transfected with pRSET containing the heparanase entire open reading frame (543 amino acids, SE ID NOs: 2 and 3), lane 3, E. coli BL21(DE3)pLysS cells transfected with pRSEThpaBK containing 414 amino acids of the heparanase open reading frame (amino acids 130-543 of SEQ ID NOs: 2 and 3), lane 4, E. coli BL21(DE3)pLysS cells transfected with pRSEThpaBH containing 302 amino acids of the heparanase open reading frame (amino acids 130-431 of SEQ ID NOs: 2 and 3), lane 5, molecular size markers, lane 6, medium of Sf21 insect cells infected with recombinant Baculovirus pFhpa containing the heparanase entire open reading frame (543 amino acids, SEQ ID NOs: 2 and 3), lane 7, Sf21 insect cells infected with recombinant baculovirus with no insert. Proteins were separated on 10% SDS-PAGE, antisera were diluted 1:1,000. Detection was performed by ECL (Amersham) according to the manufacturer's instructions. Size in kDa is shown to the right, as was determined using prestained SDS-PAGE standards, Bio-Rad, CA..

DRPR:
FIG. 18 demonstrates Western blot using affinity purified polyclonal antibodies with heparanase expressed in various expression systems. Lane 1, medium of Sf21 insect cells infected with recombinant Baculovirus pFhpa, lane 2, cell extract of a Chinese hamster ovary (CHO) clone stably transfected with a vector containing no insert, lane 3, cell extract of a CHO stable clone transfected with hpa cDNA, lane 4, proteins precipitated from medium of the yeast Pichia pastoris transfected with hpa cDNA. Proteins were separated on 4-20% gradient SDS-PAGE, antibody was diluted 1:100. Detection was performed by ECL (Amersham) according to the manufacturer's instructions. For CHO and

Pichia clones see U.S. patent application Ser. No. 09/071,618, entitled "RECOMBINANT CELLS AND METHODS FOR EXPRESSING RECOMBINANT HEPARANASE AND METHOD OF PURIFYING SAME", filed on the date of filing of the present application, which is incorporated by reference as if fully set forth herein. Size in kDa is shown to the right, as was determined using prestained SDS-PAGE standards, Bio-Rad, CA..

DEPR:
The present invention is of heparanase specific molecular probes which can be used in research and medical applications. Specifically, the present invention can be used for the detection and monitoring of malignancies, metastasis and other, non-malignant conditions, efficiency of therapeutic treatments, targeted drug delivery and therapy, using heparanase specific molecular probes, such as anti-heparanase antibodies (both poly- and monoclonal) and heparanase gene (hpa) derived nucleic acids, including, but not limited to, PCR primers, antisense oligonucleotide probes, antisense RNA probes, DNA probes and the like.

DEPR:
As used herein in the specification and in the claims section below, the term "detectable heparanase specific molecular probe" and its equivalent term "detectable heparanase molecular probe" both refer to a nucleic acid sequences hybridizable with heparanase encoding nucleic acid or to an anti-heparanase antibody capable of specifically binding heparanase. The nucleic acid sequence hybridizable with heparanase encoding nucleic acid is, for example, a synthetic oligonucleotide, an antisesnse heparanase RNA or heparanase DNA, and it is preferably labeled by the detectable moiety.

DEPR:
Therefore, according to another aspect of the present invention there is provided a method of detecting heparanase protein in a body fluid of a patient. The method comprises the steps of reacting the body fluid with an anti-heparanase antibody, either poly or monoclonal antibody, and monitoring the reaction. The body fluid is, for example, plasma, urine, pleural effusions or saliva. Monitoring the reaction may be effected by having the antibody labeled with a detectable moiety, or to use its constant region as an inherent detectable moiety, to which a second antibody which includes a detectable moiety can specifically bind.

DEPR:
According to a preferred embodiment of the present invention reacting the body fluid with the anti-heparanase antibody is effected in solution. Alternatively, reacting the body fluid with the anti-heparanase antibody is effected on a substrate capable of adsorbing proteins present in the body fluid, all as well known in the art of antibody based diagnosis.

DEPR:
As further shown in the Examples section below, protein blots and anti-heparanase antibodies prove useful in detecting the presence, absence or level of heparanase protein in various biological samples.

DEPR:
Therefore, further according to the present invention there is provided a method of detecting the presence, absence or level of heparanase protein in a biological sample. The method comprises the following steps. First, proteins are extracted from the biological sample, thereby a plurality of proteins are obtained. The protein extract may be a crude extract and can also include non-proteinacious material. Second, the proteins are size separated, e.g., by electrophoresis, gel filtration etc. Fourth, the size separated proteins are interacted with an anti-heparanase antibody, either poly or monoclonal antibody. Finally, the presence, absence or level of the interacted anti-heparanase antibody is detected. In case of gel electrophoresis the interaction with the antibody is typically performed following blotting of the size separated proteins onto a solid support (membrane).

DEPR:
Therefore, according to yet another aspect of the present invention there is provided a method of targeted drug delivery to a tissue of a patient, the tissue expressing heparanase. The method comprises the steps of providing a complex of a drug directly or indirectly linked to an anti-heparanase antibody and administering the complex to the patient. External radio imaging is also envisaged, wherein the drug is replaced with an imageable radio isotope. Endoscopic or laparoscopic imaging is also envisaged. In the latter cases the drug is typically replaced by a fluorescence or luminescence substance. These procedures may, for example, be effective in finding/destroying micrometastases.

DEPR:
Therefore, according to another aspect of the present invention there is provided a method of treating a patient having a condition associated with heparanase expression. The method comprises the step of administering an anti-heparanase antibody to the patient.

DEPR:
Preferably, the elicitation of the antibody is through in vivo or in vitro techniques, the antibody having been prepared by a process comprising the steps of, first, exposing cells capable of producing antibodies to the heparanase protein or the immonogenical part thereof and thereby generating antibody producing cells. second, fusing the antibody producing cells with myeloma cells and thereby generating a plurality of hybridoma cells each producing monoclonal antibodies, and third, screening the plurality of monoclonal antibodies to identify a monoclonal antibody which specifically binds heparanase.

DEPR:
In situ detection of heparanase by antibodies: hpa-transfected and non transfected CHO cells were plated on 8-chamber tissue culture slides (Nunc). Cells were fixed in 95% ethanol, 5% acetic acid for 5 minutes at -20.degree. C. Cells were permeabilized using permeabilization buffer (20 mM HEPES, pH 7.4; 300 mM Sucrose; 50 mM NaCl; 3 mM MgCl.sub.2 ; 0.5% Triton X-100) for 4 minutes at 4.degree. C. Endogenous peroxidases were blocked using 0.3% H.sub.2 O.sub.2 in methanol and non specific binding sites were blocked using 5% horse serum in PBS. Monoclonal anti-heparanase antibody (supernatant of hybridoma) was applied and incubated with the cells overnight at room temperature. Antibody was washed away and biotinylated secondary antibody (horse-anti mouse, Vector, Vectastain ABC system) was added for 30 minutes at room temperature. Immunostaining was detected using Di Amino Benzidine and H.sub.2 O.sub.2 (Sigma tablets) until desired staining-intensity was achieved. Slides were counterstained with Mayer's hematoxylin. Immunostaining with polyclonal antibodies was performed under the same conditions, affinity purified antibody was used at 1:500 dilution. Biotinylated horse anti-rabbit was used as a secondary antibody (Vector, Vectastain ABC system). Blood smears were prepared from a healthy donor. Fixation and staining were performed as described above.

DEPR:
This is the first result suggesting a role for heparanase in the pathogenesis of proteinuria in type I diabetes. Obviously, measurements of urinary heparanase activity is both time consuming and not sensitive enough. Moreover, we have demonstrated the presence of an inhibitor of mammalian heparanase in the urine of normal individuals. The nature of this inhibitory substance, possibly urinary glycosaminoglycans is currently being studied. Urinary heparanase activity is therefore the result of a balance between the presence in the urine of the enzyme and its inhibitor(s). Immunodetection of the heparanase protein is therefore a more sensitive and straightforward approach for diagnostic purposes. Altogether, our results clearly indicate that anti-heparanase antibodies that identify the heparanase antigen can be applied for early diagnosis of cancer metastasis and renal diseases. As discussed above, it is conceivable that heparanase may overcome the filtration barrier of the glomerular basement membrane and ECM simply by virtue of its ability to

degrade the HS moieties that are held responsible for their permeaselective properties. Urinary heparanase is therefore expected to reflect the presence of heparanase in the circulation and hence be a sensitive marker for metastatic, inflammatory and kidney disease. Of particular significance is the potential ability to follow the course of tumor progression and spread, response to anti-cancer treatments, and possible relapse of the disease in a given patient. Targeted drug delivery and therapy are another aspect of the use for such antibodies.

DEPR:
Availability of anti-heparanase antibodies will enable development of immunological assays for screening tissue and body fluids for heparanase. An ELISA will provide a more sensitive and convenient means of detection as compared to the currently available assays of heparanase activity which do not appear sensitive enough for the detection of the enzyme in non-concentrated plasma and body fluids.

☐ 5. Document ID: US 5968822 A

L1: Entry 5 of 11 File: USPT Oct 19, 1999

DOCUMENT-IDENTIFIER: US 5968822 A
TITLE: Polynucleotide encoding a polypeptide having heparanase activity and expression of same in transduced cells

BSPR:
Other potential therapeutic applications: Apart from its involvement in tumor cell metastasis, inflammation and autoimmunity, mammalian heparanase may be applied to modulate: bioavailability of heparin-binding growth factors (5); cellular responses to heparin-binding growth factors (e.g., bFGF, VEGF) and cytokines (IL-8) (31a, 29); cell interaction with plasma lipoproteins (32); cellular susceptibility to certain viral and some bacterial and protozoa infections (33, 33a, 33b); and disintegration of amyloid plaques (34). Heparanase may thus prove useful for conditions such as wound healing, angiogenesis, restenosis, atherosclerosis, inflammation, neurodegenerative diseases and viral infections. Mammalian heparanase can be used to neutralize plasma heparin. as a potential replacement of protamine. Anti-heparanase antibodies may be applied for immunodetection and diagnosis of micrometastases, autoimmune lesions and renal failure in biopsy specimens, plasma samples, and body fluids. Common use in basic research is expected.

DEPR:
Anti-heparanase antibodies, which may be raised against the recombinant enzyme, would be useful for immunodetection and diagnosis of micrometastases, autoimmune lesions and renal failure in biopsy specimens, plasma samples, and body fluids. Such antibodies may also serve as neutralizing agents for heparanase activity.

DEPR:
The recombinant protein may be purified by any conventional protein purification procedure close to homogeneity and/or be mixed with additives. The recombinant protein may be manufactured using any of the cells described above. The recombinant protein may be in any form. It may be in a crystallized form, a dehydrated powder form or in solution. The recombinant protein may be useful in obtaining pure heparanase, which in turn may be useful in eliciting anti-heparanase antibodies, either poly or monoclonal antibodies. and as a screening active ingredient in an anti-heparanase inhibitors or drugs screening assay or system.

☐ 6. Document ID: US 5362641 A

L1: Entry 6 of 11 File: USPT Nov 8, 1994

DOCUMENT-IDENTIFIER: US 5362641 A
TITLE: Heparanase derived from human Sk-Hep-1 cell line

DRPR:
FIG. 6: Preparative native PAGE. Active fractions eluted from Con-A-Sepharose were pooled, dialyzed and applied to a native 8% polyacrylamide gel. The gel was cut into 5 mm strips (0-8) and heparanase activity in material electroeluted from each strip was assayed by gel filtration on Sepharose 6B of labeled degradation products released from sulfate labeled ECM. Material associated with strip #7 was injected into rabbits to produce the polyclonal anti-heparanase antibodies used in FIGS. 5AI through 5DII:

DRPR:
FIGS. 7A and 7B: Identification of heparanase in extracts of a biopsy specimen from a human ovarian tumor. Ovarian tumor removed at surgery was homogenized and the supernatant fraction subjected to FPLC gel filtration on superose 12 column. The starting material (lane 1) and fractions number 16-19 of the active peak (lanes 2-5) were subjected to SDS/PAGE and "Western" blot analysis. FIG. 7A: Coomassie blue staining of proteins electrotransferred to Immobilon-P transfer membrane. FIG. 7B: Autoradiogram of the same transfer membrane following successive incubations with rabbit anti-heparanase antibodies and .sup.125 I-goat anti-rabbit IgG.

DEPR:
In order to obtain a single band preparation, enzyme eluted from Con A-Sepharose was subjected to native polyacrylamide gel electrophoresis, as described in Materials and Methods. The gel was cut into strips of 5 mm, and protein was electroeluted from 5 mm segments of each strip. Heparanase activity, measured by gel filtration analysis of sulfate-labelled degradation products, was eluted primarily from strip #7. A much lower activity was detected in strip #4 (FIG. 6). Enzyme associated with strip #7 was homogenized with the polyacrylamide in a minimal volume of PBS, mixed with complete Freund's adjuvant, and injected into rabbits to produce polyclonal anti-heparanase antibodies. This material will also be subjected to amino acid sequencing for the purpose of gene cloning and expression. The anti-heparanase antibodies have been used to immunodetect the enzyme in "Western" blots of fractions eluted from CD-Sephadex (FIG. 5AII(B)) and Con-A Sepharose and in active fractions derived from a biopsy specimen of a human ovarian tumor (FIGS. 7A and 7B).

☐ 7. Document ID: AU 200028786 A, WO 200052178 A1

L1: Entry 7 of 11 File: DWPI Sep 21, 2000

DERWENT-ACC-NO: 2000-579289
DERWENT-WEEK: 200065

TITLE: New polynucleotides encoding a polypeptide having heparanase activity, useful in wound healing and in gene therapy, particularly in treating tumor, inflammation, autoimmunity, neurodegenerative diseases

ABTX:
in vivo eliciting of anti-heparanase antibodies comprising administering the nucleic acid construct of (1) including a segment of the novel polynucleotide; and

ABTX:
(11) a DNA vaccine for eliciting in vivo anti-heparanase antibodies comprising the nucleic acid construct of (1) and a promoter for directing the expression of the polynucleotide segment in vivo.

ABTX:
USE - The polynucleotide is useful in gene therapy, particularly in treating tumor, inflammation or autoimmunity. Particularly, the polynucleotide is useful in modulating the bioavailability of heparin-binding growth factors, cellular responses to heparin-binding growth factors (e.g. bFGF) and cytokines (e.g. interleukin (IL)-8), cell interaction with plasma lipoproteins, cellular susceptibility to certain viral and some bacterial and protozoa infections, or disintegration of neurodegenerative plaques. The polynucleotide is useful in wound healing (e.g. thermal, chemical or radiation burns), and in the treatment of angiogenesis, restenosis, atherosclerosis, inflammation, neurodegenerative diseases (Gerstmann-Straussler Syndrome or Creutzfeldt-Jakob disease), and some viral, bacterial or protozoa infections. The polynucleotide is also useful in developing diagnostic assays for these diseases, for providing new tools for basic research especially in the field of medicine and biology, and for developing new drugs to inhibit these diseases. The nucleic acid constructs or vectors, antisense oligonucleotides, and ribozymes are useful for modulating heparanase. The polynucleotide sequences can be used to provide DNA vaccines that will elicit in vivo anti-heparanase antibodies. The polypeptide is useful for catalyzing the degradation of heparan sulfate in an in vitro assay. The recombinant proteins are also useful for obtaining pure heparanase, which in turn may be useful in eliciting anti-heparanase antibodies, either poly- or monoclonal antibodies (for immunodetection), and as a screening active ingredient in an anti-heparanase inhibitors or drugs screening assay or system.

☐ 8. Document ID: NO 200102190 A, WO 200025817 A1, AU 200013314 A

L1: Entry 8 of 11 File: DWPI Jun 12, 2001

DERWENT-ACC-NO: 2000-399323
DERWENT-WEEK: 200141

TITLE: New monoclonal antibody comprising heparanase neutralizing activity, useful for treating a condition associated with heparanase expression e.g. preventing angiogenesis

ABTX:
NOVELTY - Treating a condition associated with heparanase expression comprises administering an anti-heparanase monoclonal antibody having heparanase neutralizing catalytic activity.

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

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☐ 9. Document ID: EP 1054980 A1, WO 9940207 A1, AU 9928319 A

L1: Entry 9 of 11 File: DWPI Nov 29, 2000

DERWENT-ACC-NO: 1999-494300
DERWENT-WEEK: 200063

TITLE: New heparanase polypeptide useful for treating autoimmune diseases, skin diseases, cardiovascular diseases and nervous system diseases including Alzheimer's disease

ABTX:
USE - The heparanase protein or the anti-heparanase antibody are used in pharmaceutical compositions for treating warm blooded animals suffering from a disease resulting from shortage/lack of the heparanase protein, or from excessive activity/over-expression of the heparanase protein, respectively. The heparanase protein is used in treating diseases such as trauma, autoimmune disease, skin diseases, cardiovascular diseases and nervous system diseases including Alzheimer's disease resulting from shortage or lack of polypeptide.

ABTX:
The anti-heparanase antibody is used in treating the diseases like cancer, cancer metastasis, angiogenesis and inflammation including arthritis resulting from excessive activity or over expression of heparanase protein. The polynucleotide coding for the polypeptide is used in gene therapy strategy (claimed). The anti-heparanase antibody can be used to detect the presence or absence of polypeptide and its concentration. Hence the anti-heparanase antibodies are used as diagnostic markers for the disorders such as cancer, cancer metastasis and angiogenesis. Agonist and antagonist can replace heparanase protein and anti-heparanase antibody respectively to treat the diseases caused by increased or decreased expression of heparanase protein.

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

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☐ 10. Document ID: AU 735116 B, WO 9911798 A1, AU 9891258 A, US 5968822 A, NO 9906228 A, EP 998569 A1, CZ 200000754 A3, HU 200002675 A2, CN 1272886 A

L1: Entry 10 of 11 File: DWPI Jun 28, 2001

DERWENT-ACC-NO: 1999-302255
DERWENT-WEEK: 200142

TITLE: New human polynucleotide useful for treating angiogenesis, restenosis, and inflammation

ABTX:
USE - The recombinant protein is used as a modulator of heparin-binding growth factors, cellular responses to heparin-binding growth factors and cytokines, cell interaction with plasma lipoproteins, cellular susceptibility to viral, protozoal and bacterial infections or disintegration of neurodegenerative plaques (claimed). Heparanase may be useful for conditions such as wound healing, angiogenesis, restenosis, atherosclerosis, inflammation, neurodegenerative diseases, and viral infections. Mammalian heparanase can be used to neutralize plasma heparin, and anti-heparanase antibodies may be applied for immunodetection and diagnosis of micrometastases, autoimmune lesions, and renal failure in biopsy specimens, plasma samples, and body fluids.

ABEQ:
USE - The recombinant protein is used as a modulator of heparin-binding growth factors, cellular responses to heparin-binding growth factors and cytokines, cell interaction with plasma lipoproteins, cellular susceptibility to viral, protozoal and bacterial infections or disintegration of neurodegenerative plaques (claimed). Heparanase may be useful for conditions such as wound healing, angiogenesis, restenosis, atherosclerosis, inflammation, neurodegenerative diseases, and viral infections. Mammalian heparanase can be used to neutralize plasma heparin, and anti-heparanase antibodies may be applied for immunodetection and diagnosis of micrometastases, autoimmune lesions, and renal failure in biopsy specimens, plasma samples, and body fluids.

Full | Title | Citation | Front | Review | Classification | Date | Reference

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